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

Yasuo YOSHIOKA1,*, Osamu SUZUKI2, Kazuo NISHIMURA3, Hitoshi INOUE4, Tsuneo HARA4, Ken YOSHIDA5, Atsushi IMAI6, Akira TSUJIMURA7, Norio NONOMURA7 and Kazuhiko OGAWA1

1Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
2Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan
3Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan
4Department of Urology, Ikeda City Hospital, 3-1-18 Jonan, Ikeda, Osaka 563-8510, Japan
5Department of Radiation Oncology and Institute for Clinical Research, National Hospital Organization Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-ku, Osaka 540-0006, Japan
6Department of Radiation Oncology, Sumitomo Hospital, 5-3-20 Nakanoshima, Kita-ku, Osaka 530-0005, Japan
7Department of Urology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
*Corresponding author. Tel: +81-6-6879-3482; Fax: +81-6-6879-3489; Email: yoshioka@radonc.med.osaka-u.ac.jp

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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. Deamaley 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
| Adverse Event       | Grade 1                                                                 | Grade 2                                                                 | Grade 3                                                                 | Grade 4                                                                 | Grade 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                                                                   |
| Renal and urinary disorders |
| 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.  

Renal and urinary disorders

| Adverse Event | Grade | 1 | 2 | 3 | 4 | 5 |
|---------------|-------|---|---|---|---|---|
| Urinary tract pain | Mild pain | Moderate pain; limiting instrumental ADL | Severe pain; limiting self care ADL | – | – |
| Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract. | | | | | |
| Urinary urgency | Present | Limiting instrumental ADL; medical management indicated | – | – | – |
| Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract. | | | | | |
| Urine discoloration | Present | – | – | – | – |
| Definition: A disorder characterized by a sudden compelling urge to urinate. | | | | | |
| 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

| Adverse Event             | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 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
| Adverse Event                  | Grade | Grade | Grade | Grade | Grade |
|-------------------------------|-------|-------|-------|-------|-------|
|                                | 1     | 2     | 3     | 4     | 5     |
| **Anal ulcer**                |       |       |       |       |       |
| Asymptomatic; clinical or     |       |       |       |       |       |
| diagnostic observations only; |       |       |       |       |       |
| intervention not indicated    |       |       |       |       |       |
| **Definition:** A disorder    |       |       |       |       |       |
| characterized by a narrowing |       |       |       |       |       |
| of the lumen of the anal      |       |       |       |       |       |
| canal.                       |       |       |       |       |       |
| **Constipation**              |       |       |       |       |       |
| Occasional or intermittent   |       |       |       |       |       |
| symptoms; occasional use of   |       |       |       |       |       |
| stool softeners, laxatives,   |       |       |       |       |       |
| dietary modification, or enema|       |       |       |       |       |
| **Definition:** A disorder    |       |       |       |       |       |
| characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal. |       |       |       |       |       |
| **Diarrhea**                  |       |       |       |       |       |
| Increase of <4 stools per day |       |       |       |       |       |
| over baseline; mild increase in |       |       |       |       |       |
| ostomy output compared to     |       |       |       |       |       |
| baseline                     |       |       |       |       |       |
| **Definition:** A disorder    |       |       |       |       |       |
| characterized by irregular and infrequent or difficult evacuation of the bowels. |       |       |       |       |       |
| **Fecal incontinence**        |       |       |       |       |       |
| Occasional use of pads required |       |       |       |       |       |
| **Definition:** A disorder    |       |       |       |       |       |
| characterized by frequent and watery bowel movements. |       |       |       |       |       |
| **Hemorrhoidal hemorrhage**   |       |       |       |       |       |
| Mild; intervention not         |       |       |       |       |       |
| indicated                    |       |       |       |       |       |
| **Definition:** A disorder    |       |       |       |       |       |
| characterized by inability to control the escape of stool from the rectum. |       |       |       |       |       |
| **Grade**                     | 1     | 2     | 3     | 4     | 5     |
| indicated; TPN or hospitalization indicated |       |       |       |       |       |
| Severely altered GI function |       |       |       |       |       |
| Life-threatening consequences; |       |       |       |       |       |
| Death                        |       |       |       |       |       |
| Life-threatening consequences; |       |       |       |       |       |
| Death                        |       |       |       |       |       |
| Life-threatening consequences; |       |       |       |       |       |
| Death                        |       |       |       |       |       |
| Severe symptoms; elective    |       |       |       |       |       |
| operative intervention indicated |       |       |       |       |       |
| Transfusion, radiologic,      |       |       |       |       |       |
| endoscopic, or elective       |       |       |       |       |       |
| operative intervention indicated |       |       |       |       |       |
| Life-threatening consequences; |       |       |       |       |       |
| Death                        |       |       |       |       |       |
| Life-threatening consequences; |       |       |       |       |       |
| Death                        |       |       |       |       |       |
### Hemorrhoids

- **Definition:** A disorder characterized by bleeding from the 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

### Ileus

- **Definition:** A disorder characterized by the presence of dilated veins in the rectum and surrounding area.
- **Symptomatic:** Altered GI function; bowel rest indicated
- **Severely altered GI function:** TPN indicated
- **Life-threatening consequences:** Death

### Proctitis

- **Definition:** A disorder characterized by failure of the ileum to transport intestinal contents.
- **Rectal discomfort:** Intervention not indicated
- **Symptoms (e.g., rectal discomfort, passing blood or mucus):** Medical intervention indicated; limiting instrumental ADL

### Rectal fistula

- **Definition:** A disorder characterized by inflammation of the rectum.
- **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:** Death

### Rectal hemorrhage

- **Definition:** A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site.
- **Mild:** Intervention not indicated
- **Moderate symptoms:** Medical intervention or minor cauterization indicated
- **Transfusion, radiologic, endoscopic or elective operative intervention indicated**
- **Life-threatening consequences:** Death

### Rectal mucositis

- **Definition:** A disorder characterized by bleeding from the rectal wall and discharge from the anus.
- **Asymptomatic or mild symptoms:** Intervention not indicated
- **Symptomatic:** Medical intervention indicated; limiting instrumental ADL
- **Severe symptoms:** Limiting self care ADL
- **Life-threatening consequences:** Death

### Rectal necrosis

- **Definition:** A disorder characterized by inflammation of the mucous membrane of the rectum.
- **Tube feeding or TPN indicated:** Life-threatening consequences; Death

### Rectal obstruction

- **Definition:** A disorder characterized by a necrotic process occurring in the rectal wall.
- **Asymptomatic:** Clinical or diagnostic observations only; intervention not indicated
- **Symptomatic:** Altered GI function
- **Hospitalization indicated:** Life-threatening consequences; Death
| Adverse Event                          | Grade                                                                 |
|---------------------------------------|----------------------------------------------------------------------|
|                                       | 1                        | 2                        | 3                        | 4                        | 5                        |
| diagnostic observations only; function; limiting instrumental ADL | elective operative intervention indicated; limiting self care ADL; disabling | urgent operative intervention indicated | –                        | –                        |
| Rectal perforation                    | Symptomatic; medical intervention indicated                            | Severe symptoms; elective operative intervention indicated | Life-threatening consequences; Death | Death                    |
| Rectal stenosis                       | Symptomatic; altered GI function                                        | Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated | Life-threatening consequences; Death | Death                    |
| Rectal ulcer                          | 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; Death | Death                    |
| Gastrointestinal disorders -          | Asymptomatic or mild symptoms; clinical or diagnostic noninvasive intervention but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling | Life-threatening consequences; Death | Death                    |
| 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 | Life-threatening consequences; Death | Death                    |
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 urethrogramy 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 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 2%, 4% and 6% (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). The actuarial 2-, 3-, and 5-year Grade 1–3 rectal bleeding rates were 33%, 38% and 38%, and the corresponding figures for Grade 2–3 were 21%, 23% and 23% (P = 0.015), and the corresponding figures for Grade 2–3 were 21%, 23% and 23% (P = 0.001) (Fig. 4).


**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

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**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   |              |              | <0.001 |
| 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 gastrointestinal toxicity rate (%) | 0.083 |
| at 2 years                | 35           | 27            |     |
| at 3 years                | 38           | 31            |     |
| at 5 years                | 41           | 32            |     |
| Grade 2–3 late gastrointestinal 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             |     |

*aMean ± standard deviation.

Grade: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Late gastrointestinal toxicity included late rectal bleeding.
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
occurrence rates were 21%, 23% and 23% for 2D simulation, and
the five institutions as follows; 14
observed in the incidence rate of Grade 1 toxicity among
retrospective nature. On the other hand, a variation was
making a high degree of accuracy likely for the data collec-
tion. This suggests that our current study could still add
value to the field of study as well as improve the under-
standing of the influences on the incidence of Grade 1 toxicity.

Moreover, if we consider the third and fourth columns, the
rate of Grade 1 toxicity was 11% for 1 cm-width MLC, with
no statistically significant difference compared to the
1 cm-width MLC. 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
reviewed the patients who were the subject of this paper. This
makes a high degree of accuracy likely for the data collec-
tion, 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 ret-
rospective analysis; therefore, the significance of the figures
presented as Grade 1 toxicity should be considered as rela-
tively 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 con-
formal 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 tox-
icity 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 con-
formal radiotherapy (3D-CRT) as part of an American
Society for Radiation Oncology (ASTRO) outcomes initia-
tive. In the Task Force Conclusion, they stated that
3D-CRT reduces late morbidity, particularly GI late mor-
bidity, 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%, re-
spectively, 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%, re-
spectively, 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, arriv-
ing at the conclusion that the larger margin had been asso-
ciated 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 compris-
ing 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 hetero-
genicity 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 reproduc-
ibility. 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 clinic-
ical indicators such as V40Gy or V65Gy of the rectum, could

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).
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 × 10.2 × 8.8 cm (2D simulation) to 8.4 × 8.2 × 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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