Reduction of Irradiation Volume and Toxicities with 3-D Radiotherapy Planning over Conventional Radiotherapy for Prostate Cancer Treated with Long-term Hormonal Therapy

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Abstract. *Background: As hormonal therapy has an influence not only on outcome but also on toxicities, we compare the efficacy of three-dimensional radiotherapy planning (3D-RTP) and of conventional radiotherapy (Conv-RT) in association with long-term hormonal therapy in reducing toxicity of treatment. Patients and Methods: A retrospective case-control study was performed comparing the frequency of radiation toxicity between 63 Conv-RT and 52 3D-RTP patients with locally advanced prostate cancer (intermediate to high risk) treated with combined hormonal therapy. The average duration of neoadjuvant treatment was 7 months (1-38 months) and that of adjuvant treatment was 38 months (4-94 months). Patients were treated with 70 Gy of box field radiotherapy for the same clinical target volume (60 Gy prostate + seminal vesicle and 10 Gy boost to prostate). Results: Treatment volumes (=X_{RL}×Y_{SI}×X_{AP}, where X_{RL}=right left length of anterior-posterior portals, X_{AP}=anterior posterior length of lateral portals and Y_{SI}=superior inferior length of anterior-posterior portals) were significantly smaller in the 3D-RTP group (630±130 cm^3) than in the Conv-RT group (1036±223 cm^3) (p<0.0001). Acute side-effects in urological tracts (GU) were associated with X_{RL} (p=0.02), Y_{SI} (p=0.008) and treatment technique (Conv-RT vs. 3D-RTP: p=0.01). The frequency of acute gastrointestinal tract (GI) toxicity was associated with X_{RL} (p=0.02), X_{AP} (p=0.03). Late GU toxicities were associated with YAP (p=0.02) and X_{RL} (p=0.03). Treatment technique was the determinant of late GI toxicities (p=0.03). Frequency of late GI toxicities of G2 or more was reduced from 35% in the Conv-RT group to 15% in the 3D-RTP group (p=0.03, odds ratio=0.43). Patients with late GI toxicity received longer periods (39±19 months) of adjuvant hormonal therapy than the patients without (31±18 months, p=0.04). Prostate-specific antigen (PSA) failure-free survival rates at 3 years were 92% for the 3D-RTP group and 90% for the Conv-RT group (73% at 5 years, 67% at 10 years). Overall survival rates were 97% (3-year), 91% (5-year), and 91% (10-year) in the Conv-RT group, compared to 100% at 3 years in the 3D-RTP group. Conclusion: Long-term hormonal therapy has the potential to improve outcome but induce late GI toxicity. 3D-RTP simultaneously reduced treatment volume and frequency of acute urinary and late GI toxicities even with long-term hormonal therapy*

Conformal radiotherapy using three-dimensional treatment planning (3D-RTP) allows for more precise delivery of treatment, and unlike conventionally planned radiotherapy (Conv-RT) has a potential for sparing surrounding normal tissues. Therefore, 3D-RTP is now becoming one of the standard treatments in radiotherapy.

Many retrospective and prospective analyses of conformal radiotherapy suggested that side-effects were reduced in using 3D-RTP and a low incidence of serious toxicity was noted even when high tumor doses were used (1-12). However, most of the reports contained mixed populations with respect to prescribed dose, target volume (pelvic, seminal vesicle and prostate) and use of hormonal therapy. Therefore, Morris *et al.* determined that randomized trials and follow-up of completed trials remain necessary to address these clinical outcomes specifically with regard to patient subsets and the use of hormonal therapy (1). In Japan, hormonal therapy plays an important role in the treatment of prostate cancer

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especially for advanced disease. Androgen suppression has several aspects of influence on prostate radiotherapy. It has complicated influence on toxicity, including substantial reduction of the volume of prostate cancer, with the average rate of volume reduction reported at 37% (16). Therefore, the irradiated volume and side effects may be reduced and some authors have already reported a reduction in gastrointestinal (GI) complication rate (5). On the other hand, others reported that urinary tract (GU) side-effects and/or late rectal bleeding were intensified by hormonal treatment itself (6, 8, 13-14). Feigenberg *et al*. reported that the 5-year actuarial risk of grade 2 or higher gastrointestinal morbidity was 17% for no hormonal treatment *vs*. 18% for short term (<6 months) androgen deprivation and 26% for long-term androgen deprivation (6 months or more) (p=0.017) (14). In addition, some authors postulate the potential curative role of hormonal therapy, especially by long-term maximal androgen blockade, even for localized disease (16). With the tendency for an increasing elderly population, especially in Japan, such an issue has an increasing importance. Thus, a case-control study was performed to examine the influence of treatment technique in patients treated with a homogeneous tumor dose and fractionation scheme for the same target volume (CTV) with combined long-term hormonal therapy to avoid the influence of complicating factors.

Patients and Methods

We installed 3D-RTP on July 2003, thereafter, consecutive patients with localized but high-risk prostate cancer were treated with hormonal therapy and followed definitive radiotherapy to a dose of 70 Gy at the Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease. Informed consent was obtained in written form. We tried to comparing toxicities of 3D-RTP radiotherapy to previous historical control data in case control study. Pretreatment assessment included clinical examination, transrectal ultrasound of a prostate, laboratory test, prostate biopsy with histological evaluation, bone scan, and a lymph node evaluation by a pelvic computed tomography. Patients with metastasis, with positive lymph node metastasis, with previous pelvic irradiation, with performance status (WHO) 3 or more, and with active synchronous malignant disease were excluded.

Radiotherapy. All patients were categorized into intermediate or high-risk cancer cases and treated initially with androgen ablation treatment, which was continued during and after radiotherapy. The androgen ablation treatment mainly consisted of luteinizing hormone-releasing agonist plus an anti-androgen agent. The average duration of neoadjuvant treatment was 7 months (1-38 months), and the duration of adjuvant treatment was 38 months (4-94 months).

All patients were treated with a dose of 70 Gy to the isocenter of box fields using 20 MV photons by Linac (Clinac 2300; Varian Medical System Co., Palo Alto, CA USA) equipped with a 1 cm multileaf collimator. Conv-RT was performed between 1998 and 2001, and 3D-RTP between 2003 and 2005.

Table I. *Toxicity grading scale*.

A. Acute toxicity	
(i) Acute gastrointestinal (GI) tract toxicity	
Grade 1	Increased frequency or change in quality of bowel habit not requiring medication. Rectal discomfort not requiring medication.
Grade 2	Diarrhea requiring medication. Mucus discharge not necessitating sanitary pads. Rectal or abdominal pain requiring medication.
Grade 3	Diarrhea requiring parenteral support. Severe mucus or bloody discharge necessitating sanitary pads. Abdominal distended bowel loops.
Grade 4	Acute or subacute obstruction, fistula, or perforation. GI bleeding requiring tube decompression or bowel diversion.
(ii) Acute genitourinary (GU) toxicity	
Grade 1	Increased frequency of urination or nocturia than pretreatment habit. Dysuria, urgency not requiring medication.
Grade 2	Increased frequency of urination or nocturia, dysuria, urgency, bladder spasm requiring medication.
Grade 3	Increased frequency of urination or nocturia that is more frequent than every hour requiring catheter intervention. Dysuria, urgency, bladder spasm requiring regular, frequent narcotic. Gross hematuria with or without clot passage.
Grade 4	Hematuria requiring transfusion. Acute bladder obstruction not secondary to clot passage, ulceration, or necrosis.
B. Late toxicity	
Grade 1	Minor symptoms requiring no treatment.
Grade 2	Symptoms requiring medication (Steroid for alleviating symptom excluding Fe).
Grade 3	Hospitalization for minor intervention may be required. (Transfusion, urethral dilatation, laser coagulation and blood transfusion).
Grade 4	Major surgical intervention required (laparostomy, colostomy, cyterectomy).

The simulation for the Conv-RT involved placement of Foley catheters and contrast into the bladder and rectum. The initial treatment fields of Conv-RT involved the prostate and seminal vesicle using a four-field box technique which delivered 60 Gy at 2 Gy per fraction. Cone down technique was applied at 60 Gy using shrinking fields limited to the prostate only.

For 3D-RTP, the gross tumor volume (GTV), planning target volume (PTV), and organ at risk were outlined on each of the CT images for each patient. The large PTV was matched to the prostate gland and seminal vesicles with an 8-10 mm lateral margin, 10 mm craniocaudal and 6-15 mm anterior-posterior margins, with 5 mm leaf margin. Shrinking PTV (prostate only) was used after treating with 60 Gy up to 70 Gy using 8-10 mm lateral, 0-5 mm craniocaudal, 10-15 mm anterior and 5 mm posterior margins, with 3 mm leaf margin. Patients were treated in a supine position without any fixation device. To assure reproducibility, patients' legs were kept in the same position with a leg-rest. Data obtained with

Table II. *Patient characteristics*.

	Conv-RT (n=58)	(%)			3D-RTP (n=52)	(%)	*p*-Value
Age (years)	67.5±5.7				70±6.7		0.03
Duration of hormonal therapy							
Neoadjuvant (days)	311±200				260±193		n.s.
Adjuvant (months)	38±22				27±9		0.0009
Follow-up (months)	61 (7-96)				19 (7-45)		0.001
iPSA (ng/ml)	34.5±33.9				37.6±37		n.s.
Clinical T category							
T1	6	(10%)			5	(10%)	n.s.
T2	13	(22%)			18	(35%)	
T3	37	(64%)			24	(46%)	
T4	2	(3%)			5	(10%)	
Differentiation							
G1	5	(9%)	Gleason combined	5	1	(2%)	NA
G2	35	(60%)	score	6	3	(6%)	
G3	18	(31%)		7	15	(29%)	
				8	17	(33%)	
				9	13	(25%)	
				10	3	(6%)	
Risk group							
Unfavorable	48	(83%)			52	(100%)	0.008
Intermediate	10	(17%)					

3D-RTP: Three-dimensional radiotherapy planning, Conv-RT: conventional radiotherapy. iPSA=Initial prostate-specific antigen. Unfavorable, meet one or more condition: iPSA 20 or more, T stage 3 or more, Gleason score 8 or more. Favorable, meet all three conditions: iPSA 10 or less, well-differentiated, T stage 2 or less. Intermediate, not included in unfavorable nor favorable groups.

treatment-planning computed tomography (Hitachi W1000, Hitachi Medical Co., Tokyo, Japan) were transferred onto Cadplan (Varian Medical System Co.) or Xio (CMS Japan Co. Tokyo Japan).

Follow-up. Follow-up was conducted at intervals of at least one month during the first three months, one to three months until 2 years, and at one to six months thereafter. The median follow-up period for toxicities was 31 months (7-96 months). The acute and late toxicities caused by radiotherapy were scored in all patients (Table I). Toxicity occurring until 90 days after treatment was defined as acute toxicity and the toxicity appearing later was regarded as late toxicity. Acute toxicity was evaluated according to the modification of the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring system (Table I). Late toxicity was graded using the morbidity grading system modified by Pilepich *et al*. (17) (Table I). Prostate-specific antigen (PSA) relapse was defined as a PSA rise over 1.0 ng/ml that occurred for 3 consecutive measurements, or at the start of salvage therapy.

Statistical analysis. Student's *t*-test for normally distributed data and the Mann Whitney *U*-test for skewed data sets were used. The Chi-square test was used to compare the percentage of worst side-effects. Comparison of additional data was carried out by the Kaplan-Meier method (time to reach GI damage of grade 2 or above) and differences between treatment groups were compared with the log-rank test. Significance was defined as $p<0.05$.

Results

Background comparisons were made on the different treatment methods. Significant findings were higher age, shorter follow-up periods and more patients at high risk in the 3D-RTP than in the Conv-RT group (Table II).

Field length and treatment volume of radiation therapy without consideration of the blocked area were analyzed. The reductions in treatment fields and volume by 3D-RTP over Conv-RT are shown in Table III. Average anterior-posterior portals were 10.5 cm (X_{RL}) × 10.5 cm (Y_{SI}) for Conv-RT planning, compared with 8.7 cm × 8.7 cm for 3D-RTP ($p<0.0001$). Average lateral portals (X_{AP}) were also reduced by using 3D-RTP from 9.3 cm × 10.4 cm to 8.3 cm × 8.8 cm ($p<0.0001$). The average treatment volume ($X_{RL}\times Y_{SI}\times X_{AP}$)

Table III. *Comparison of field size and volume between different treatment planning.*

	Conv-RT (n=63)	3D-RTP (n=52)	*p*-Value
AP portals (cm)			
X axis (X_{RL})	10.5±1.1	8.7±0.7	<0.0001
Y axis (Y_{SI})	10.5±1.0	8.7±0.9	<0.0001
Lateral portals (cm)			
X axis (X_{AP})	9.3±0.8	8.3±0.8	<0.0001
Y axis	10.4±1.1	8.8±0.9	<0.0001
Volume (X_{RL}*Y_{SI}*X_{AP}) (cm^3)	1036±223	630±130	<0.0001

AP: anterior-posterior; X_{RL}=(right-left) horizontal length of AP portals, X_{AP}=anterior-posterior length of lateral portals,Y_{SI}=vertical length of AP portals.

Table IV. *Comparison of toxicity between different treatment planning*

	Conv-RT (n=63)		3D-RTP (n=52)		*p*-Value
Acute urinary toxicity					
–	5	(9%)	12	(23%)	
+	53	(91%)	40	(77%)	0.06
Acute gastrointestinal tract toxicity					
–	7	(12%)	13	(25%)	
+	51	(88%)	39	(75%)	0.13
Late urinary toxicity					
–	34	(59%)	42	(81%)	
+	24	(41%)	10	(19%)	0.02
Late gastrointestinal toxicity					
–	17	(29%)	29	(56%)	
+	41	(71%)	23	(44%)	0.009

+, Grade 1+2+3+4; –, no symptom.

decreased by 61% from 1,036±223 cm^3 to 630±130 cm^3 (p<0.0001) using 3D-RTP.

Side-effects. 3D-RT groups showed fewer side-effects in late GI (p=0.009) and late GU toxicities (p=0.02) (Table IV).

On detailed analysis, the frequency of acute GU side-effects were associated with X_{RL} (p=0.02), Y_{SI} (p=0.008), treatment volume (p=0.02) and treatment technique (Conv-RT *vs*. 3D-RTP: p=0.01) (Table VA). Frequencies of acute GI tract toxicities were associated with X_{RL} (p=0.02) and X_{AP} (p=0.03, Table VB). Late GU toxicities were associated with Y_{SI} (p=0.02) and X_{AP} (p=0.03) (Table VC), and symptoms of grade 2 or more occurred in 8% of patients treated by Conv-RTP and in 2% of patients treated by 3D-RTP although this difference was of borderline significance (p=0.06).

Treatment technique was a determinant of late GI toxicity (p=0.03, Table VD). Late GI side-effects of grade 2 or more appeared in 35% of patients treated with Conv-RT compared to 15% of patients treated with 3D-RTP (p=0.03, odds ratio=0.43). Duration of adjuvant hormonal therapy was also a significant determinant of late GI toxicities. Patients with late GI toxicity received longer periods (39±19 months) of adjuvant hormonal therapy than those without (31±18 months, p=0.04). Cumulative probabilities of being free from GI complications of grade 2 or more were 81% and 66% at 2 years for 3D-RTP and Conv-RT groups (61% at 8-years), respectively (Figure 1, n.s).

Six cases of severe GI side-effects of grade 3 or more were observed. Of these, one case of grade 4 with rectal ulceration requiring surgery occurred 5 months after completion of Conv-RT. The remaining five patients showed grade 3 rectal bleeding and required hospitalization. Of these five, two received laser coagulation and required blood transfusions, while two patients showed ulcer formation. One other patient underwent laser coagulation and resulting in rectal stenosis required balloon dilatation. Of these 6 cases, all except one patient were in the Conv-RT group.

PSA failure and survival. PSA failure-free survival rates at 3 years were 92% for the 3D-RTP group and 90% for the Conv-RT group (73% at 5-years, 67% at 10-years in the Conv-RT group). Overall survival rates were 97% (3-years), 91% (5-years) and 91% (10-years) in the Conv-RT group, whereas it was 100% at 3-years in the 3D-RTP group (n.s.). Four patients died of prostate cancer at 4, 12, 47 and 69 months after radiotherapy in the Conv-RT group, while thus far no fatalities due to prostate cancer have been recorded in the 3D-RTP group.

Discussion

Prostate cancer is the most commonly diagnosed cancer among males in the USA, and probably in Europe as well as in Japan, as the biochemical detection of early prostate cancer with PSA becomes a common laboratory test. In recent years, a remarkable increase in the number of patients with prostate cancer, especially in the elderly, has been noted. Until the late 1990's, Japanese urologists managed prostate cancer mainly by surgery combined with hormonal therapy, pre- or postsurgery, or in combination. Hormonal therapy alone is also an alternative in Japan, where 45% of 2,671 registered cases were treated by hormonal therapy alone, even with localized disease in 2000 (8). This number rose to 60% in elderly patients of 70 years or older (8). With the trend of an increasing number of elderly patients, radiotherapy has become one of

Table V. *Influence of field size and volume on toxicities*.

A. Acute urinary toxicity

Variable	Strata	G0 (n=17)	(%)	G1 (n=83)	(%)	G2 (n=10)	(%)	*p*-Value
AP portals (cm)	X_{RL}	8.9±1.04		9.7±1.7		10.3±2.4		0.02
	Y_{SI}	8.8±1.1		9.7±1.7		10.4±0.9		0.008
Lateral portals (cm)	X_{AP}	8.6±1.1		8.8±1.0		9.0±0.8		n.s.
Volume (X_{AP}*Y_{AP}*X_{RL}) (cm^3)		686±186		859±283		976±239		0.02
Treatment technique	Conv-RT	5	(9%)	44	(76%)	9	(15%)	0.01
	3D-RTP	12	(23%)	39	(75%)	1	(2%)	

B. Acute gastrointestinal tract toxicity

Variable		G0 (n=20)	(%)	G1 (n=53)	(%)	G2 (n=37)	(%)	*p*-Value
AP portals (cm)	X_{RL}	9.2±1.2		9.7±1.4		9.8±1.3		n.s.
	Y_{SI}	8.9±1.4		9.8±1.2		9.9±1.3		0.02
Lateral portals (cm)	X_{AP}	9.0±1.4		9.8±1.2		9.9±1.3		0.03
Volume (X_{AP}*Y_{AP}*X_{RL}) (cm^3)		724±265		869±290		870±248		0.09
Treatment technique	Conv-RT	7	(12%)	29	(50%)	22	(38%)	n.s.
	3D-RTP	13	(25%)	24	(46%)	15	(29%)	

C. Late urinary toxicity

Variable	Strata	G0 (n=76)	(%)	G1 (n=28)	(%)	G2 (n=3)	(%)	G3 (n=3)	(%)	*p*-Value
AP portals (cm)	X_{RL}	9.5±1.3		10. 0±1.0		9.4±2.0		10.7±2.3		n.s.
	Y_{SI}	9.3±1.2		10.4±1.2		9.9±1.2		11.7±1.5		0.02
Lateral portals (cm)	X_{AP}	9.4±1.2		10.4±1.2		9.9±1.2		11.0±2.6		0.03
Volume (X_{AP}*Y_{AP}*X_{RL}) (cm^3)		782±245		976±274		829±300		1165±473		0.09
Treatment technique	Conv-RT	34	(59%)	19	(33%)	2	(3%)	3	(5%)	0.06
	3D-RTP	42	(81%)	9	(17%)	1	(2%)	0	(0%)	

D. Late gastrointestinal toxicity

Variable	Strata	G0 (n=46)	(%)	G1 (n=35)	(%)	G2 (n=24)	(%)	G3- (n=5)	(%)	*p*-Value
AP portals (cm)	X_{RL}	9.4±1.3		9.7±1.3		9.9±1.5		9.8±1.3		n.s.
	Y_{SI}	9.5±1.4		9.6±1.2		9.9±1.3		10.4±1.7		n.s.
Lateral portals (cm)	X_{AP}	8.6±0.9		8.9±1.0		9.0±1.0		9.1±0.9		n.s.
Volume (X_{AP}*Y_{AP}*X_{RL}) (cm^3)		797±288		843±243		908±288		950±299		n.s.
Treatment technique	Conv-RT	17	(29%)	20	(34%)	17	(29%)	4	(8%)	0.03
	3D-RTP	29	(56%)	15	(29%)	7	(13%)	1	(2%)	

the major treatment modalities. In Japan, many institutes have used hormonal therapy for prostate cancer patients, especially for advanced disease, and when combined with radiotherapy it not only influences disease outcomes but also the side-effects (19). Several authors hypothesized that adjuvant hormonal therapy slows the reparative process of the irradiated rectum, thereby increasing the susceptibility for developing a late rectal injury (14, 15). However, we were unable to find any randomized data comparing Conv-RT and 3D-RTP with combined long-term hormonal therapy. To facilitate the comparison, patients were chosen who were treated with the same target volume and hormonal therapy (70 Gy box field irradiation intended to treat prostate and seminal vesicle) except for the treatment planning technique.

Basically, the most severe complications of rectal irradiation have been eliminated using a conformal technique in the last decade. Moreover, fewer acute toxic effects and an acceptable

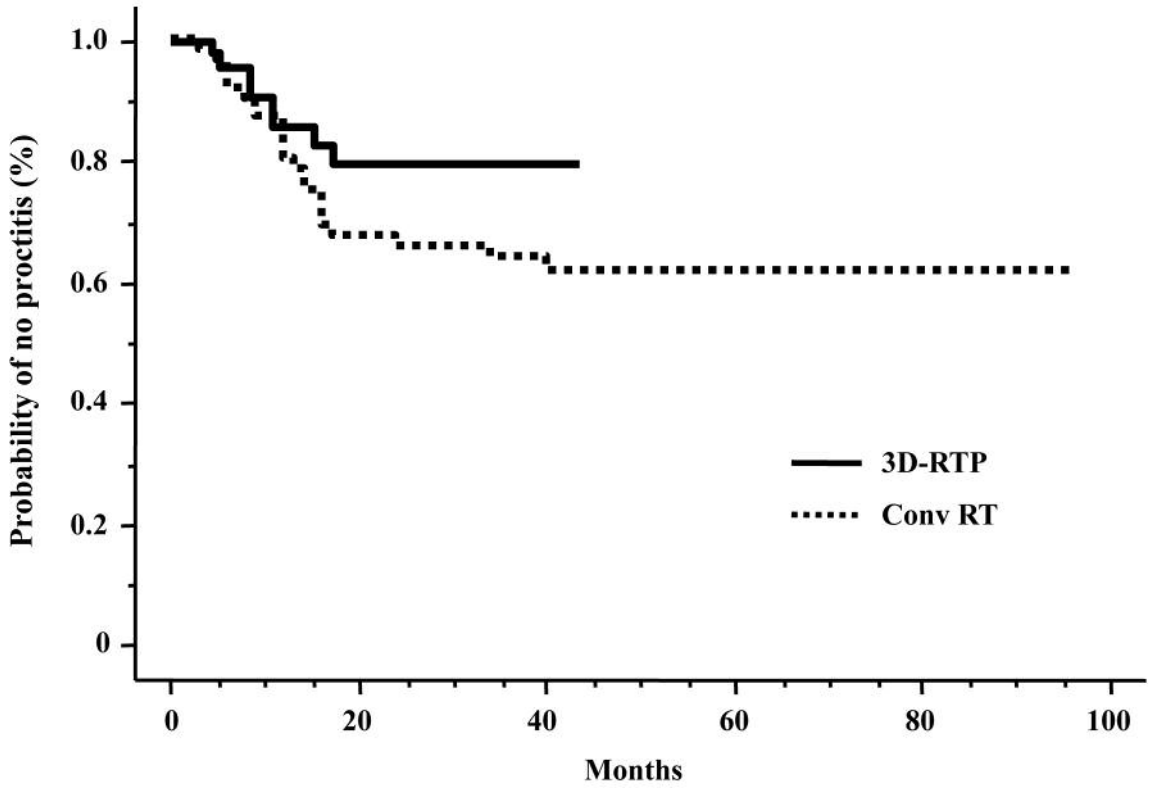

Figure 1. *Cumulative incidence of rectal bleeding grade 2 or more. Cumulative probabilities of being free from rectal bleeding of grade 2 or more were 81% and 66% at 2 years for 3D-RTP and Conv-RT groups, respectively (p=0.19, n.s.).*

degree of late side-effects have been obtained even when the dose for treatment of prostate cancer was increased from the standard 64-66 Gy to 75 Gy or more (20). GI complications of conformal radiotherapy of prostate cancer now include rectal bleeding associated with telangiectatic changes to the vasculature of the submucosa and, in severe cases, ulceration requiring cautery procedures and or transfusion. Hanks *et al*. reported that treatment volume and technique were the important factors for late rectal side-effects (22). Koper *et al*. reported 10% of patients with moderate to severe rectal bleeding in a 3-year follow-up after 66 Gy of RT (3). Dearnaley *et al*. reported that fewer men developed radiation-induced proctitis and bleeding RTOG grade 2 or more in the conformal group (5%) than in the conventional group (15%, p=0.01) in a randomized controlled trial that included 225 men treated with 64 Gy (2). Smit *et al*. reported that the 2-year incidence of moderate or severe proctitis after conventional radiotherapy was 20-22% for anterior rectal doses less than 75 Gy, but increased to 60% when the dose was more than 75 Gy (21). Our data (for grade 2 or more: 35% late rectal toxicity in the Conv-RT arm and 15% in the 3D-RTP arm) concur with these data in reduction of morbidity using 3D-RTP. A relative high morbidity ratio (39% at 8-years in Conv-RT group) may partly be due to usage of long-term hormonal therapy (14). Because of the retrospective nature of our study, we were limited to the use of the old morbidity grading system. However, our data revealed that a 1 cm wider field resulted in a 1.5-fold larger volume and elevated the side-effect rates with long-term hormonal treatment (1, 4, 8).

Several randomized trials have shown no significant difference in the occurrence of acute/late GU toxicity between conventional and conformal radiotherapy (1-3). On the other hand, Yoshimura *et al*. reported that PTV length (craniocaudal length of PTV) is a determinant of early GU side-effects (13). Schultheiss *et al*. reported that 4.6% of late GU toxicity in conventional RT was reduced to 0.2% in an analysis of 616 patients treated by 3D-CRT (5). Vavassori *et al*. reported that larger irradiated volumes were associated with frequency of urination, tenesmus, incontinence and bleeding, which our data are in agreement with (8). We also confirmed the importance of each field length in addition to the irradiated volume. The craniocaudal length of irradiated portals (Y_{SI}) is a useful determinant factor in acute lower GI, GU and late GU toxicities. In addition, frequency of acute GU and GI toxicities were correlated with the horizontal width of anterior-posterior portals (X_{RL}: p=0.02 and 0.03).

Patients with unfavorable prognostic features, who may have micrometastatic disease, are not ideal candidates for dose-escalation studies and should be treated by combination treatment. It is well known that radiation dose is a strong, independent predictor of failure (25). However, if radiation therapy is combined with long-term androgen ablation, which may have synergistic effects with radiation therapy (23), a higher dose may not have a major impact on local control. Nakamura *et al*. reported a relapse-free survival rate of 86.1% using a median dose of 65 Gy with hormonal therapy in a Japanese Pattern of Care Study (23, 24). Our results of 90% or more PSA failure-free survival rates and overall survival of nearly 100% at 5 years concur with their data and suggest the possibility of combined treatment. Although it cannot be concluded that survival outcome with hormonal therapy is superior to that of others, many Japanese radiation oncologists may consider that the higher dose levels (>72 Gy) are not always necessary when combined with long-term hormone treatment, especially in elderly patients (24). In addition, some authors postulate the potential curative role of hormonal therapy, especially by long-term maximal androgen blockade, even for localized disease (16). If this strategy is worthwhile, our data can provide baseline data of toxicities and survival outcome.

In conclusion, long-term hormonal therapy has the potential to improve outcome but may induce late GI tract toxicity. 3D-RTP simultaneously reduced treatment volume and frequency of acute urinary and late GI toxicities even with long-term hormonal therapy.

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