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Longitudinal comparison of quality of life after real-time tumor-tracking intensity-modulated radiation therapy and radical prostatectomy in patients with localized prostate cancer

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The purpose of this study was to compare the quality of life (QOL) in patients with localized prostate cancer (PC) after intensity-modulated radiation therapy assisted with a fluoroscopic real-time intensity-modulated radiation therapy (RT-IMRT) tumor-tracking system versus the QOL after radical prostatectomy (RP). Between 2003 and 2006, 71 patients were enrolled in this longitudinal prospective study. Each patient was allowed to decide which treatment modality they would receive. Of the 71 patients, 23 patients underwent RT-IMRT, while 48 opted for RP. No patient received neo-adjuvant or adjuvant hormone therapy. The global QOL and disease-specific-QOL were evaluated before treatment and again at 1, 3 and 5 years after treatment. There was no significant difference in the background characteristics between the two groups. The 5-year biochemical progression-free survival was 90% in the RT-IMRT and 79% in the RP group. In the RT-IMRT group, there was no significant deterioration of the global QOL or disease-specific QOL through 5 years post-treatment. In the RP group, the urinary function, sexual function, and sexual bother indicators significantly deteriorated after treatment. Urinary and sexual function was significantly better in the RT-IMRT group at 1, 3 and 5 years post-treatment compared to the RP group. RT-IMRT may be a preferable treatment for localized PC because of similar efficacy to RP but better post-treatment QOL.

Keywords: intensity-modulated radiation; radical prostatectomy; QOL; real-time tumor-tracking; image-guided radiotherapy

INTRODUCTION

External irradiation therapy is performed as a standard treatment in patients with localized prostate cancer (PC). Recent advances in clinical radiation technology allow high-accuracy external therapies such as intensity-modulated radiation therapy (IMRT). Studies using IMRT for high-dose irradiation to treat localized PC report decreased incidence of adverse events and favorable clinical outcomes [1]. However, adverse events may occur even in patients during high-accuracy radiotherapy due to organ (prostate) motion during radiation therapy. We previously implemented RT-IMRT tumor-tracking by inserting gold markers to correct for organ motion and setup errors in these patients [2, 3]. We reported RT-IMRT was associated with a decrease in the incidence of adverse events and potent anti-tumor effects upon short-term follow-up [4]. However, it is unknown whether RT-IMRT leads to improved quality of life (QOL) over long periods of time. To investigate the influence of RT-IMRT on the health-related QOL (Hr-QOL) to that of radical

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prostatectomy (RP), we conducted a longitudinal study to compare the global Hr-QOL, PC disease-specific QOL, and emotional health in patients with localized PC who underwent RT-IMRT or RP in our hospital.

MATERIALS AND METHODS

Patients with local prostate cancer (PC) ($n = 108$) were referred to the Department of Urology at our hospital between April 2003 and March 2006. A total of 71 patients had not previously received endocrine therapy and were enrolled in this longitudinal prospective study. Pathological findings for all patients were evaluated by a central pathologist at our hospital. The Gleason score, positive core count, and tumor area as a percentage of the positive core were measured. Staging was performed with computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy. Additionally, D'Amico's risk classification was conducted using the serum prostate-specific antigen (PSA) level at the time of diagnosis [5]. The treatment modality (RT-IMRT or RP) to be used was chosen by each patient after thorough discussion of each with urologists and radiation oncologists. Informed consent was obtained from each patient. This study was conducted in accordance with the Institutional Review Board of our hospital and the ethical standards of the Helsinki Declaration (1964, amended most recently in 2000) of the World Medical Association.

For RT-IMRT, three gold markers (2.0 mm in diameter) were inserted into the prostate gland prior to treatment planning by CT. One marker was inserted at the apex of the prostate and others were inserted at the left and right of the base of the gland. Details of this protocol have been reported previously [3]. The position of the markers can be visualized during irradiation and their positions indicated by the 3D radiation treatment-planning system are superimposed on the two sets of fluoroscopic images on the display unit of the RT-IMRT system. Details regarding calculation of the parallel and rotational setup error have been reported previously [3]. Patients were treated with 75 Gy in 30 fractions at the isocenter, with the exception of patients with unfavorable general conditions or those receiving anticoagulants. These patients were alternatively treated with 70 Gy in 28 fractions. Xio (CMS, and St Louis, MO) was used for treatment planning. Radical prostatectomy was performed with an open or laparoscopic approach. The decision to perform a nerve-sparing procedure depended on preoperative factors (Gleason score, number of the positive biopsy cores, PSA level, and patient preference).

Survival rates were calculated using the Kaplan-Meier method. The day of initial treatment was Day 0 and the day of death or final observation was the endpoint. Biochemical progression-free survival (bPFS) was also calculated using the Kaplan-Meier method, the day of initial treatment was Day 0 and endpoints were either the day of progression established by the Pheonix criteria for patients receiving RT-IMRT [6], or for patients receiving RP, the day on which PSA levels that were below the detection limit after surgery returned to 0.2 ng/ml or the final day of observation. The results were compared between each group using the Log-rank test.

We evaluated the global Hr-QOL with the Short Form 36-Item Health Survey (SF-36) [7]. The questionnaire measured eight domains—four physical and four emotional. The value of each domain was converted into a norm-based score (NBS) by correcting the mean of each domain to 50 points and the standard deviation to 10 points. Using these values makes it possible to compare those of each group with the average Hr-QOL in Japanese [7]. The University of California, Los Angeles, Prostate Cancer Index (UCLA-PCI) was used to evaluate the prostate-specific QOL. The UCLA-PCI is a previously-established scoring system for a prostate cancer patient's disease-specific QOL and evaluates function and bother with respect to three aspects of QOL: urinary, bowel and sexual activity [8]. Scores range from 0–100 points, where higher scores reflect better QOL. We also evaluated mental QOL with the Hospital Anxiety and Depression (HAD) Scale [9]. The HAD scale assessed anxiety and depression in patients and consisted of seven questions with scores ranging from 0–21. All questionnaires were mailed to patients before treatment and again at 1, 3 and 5 years post-treatment. Patients completed the questionnaires and returned them by mail.

We performed longitudinal QOL analyses to compare QOL for each treatment arm over time. The Hr-QOL data were incomplete for some patients and the Last Value Carried Forward (LVCF) method was used to compensate for missing data. Repeated measures analysis of variance (ANOVA) followed by Dunnett's multiple comparison test was used to examine differences between QOL scores within each treatment arm over time. In addition, Mann-Whitney U-tests were used to compare the scores of each domain in the SF-36, the UCLA-PCI, and the HAD scale between each treatment group at baseline, 1 year, 3 years and 5 years after treatment. All P values were two-tailed and values $P < 0.05$ were considered significant.

RESULTS

Study population, treatments and adverse effects

Table 1 outlines background characteristics of the patients evaluated in this study. Of the 71 patients, 23 underwent RT-IMRT. The radiation dose of RT-IMRT was 75 Gy/30 fractions in 15 patients, and 70 Gy/28 fractions in 8 patients. The remaining 48 patients underwent RP using laparoscopic approaches in 30 patients and open approaches in 18 patients. Bilateral nerve-sparing was performed in 13 of the 48 patients receiving RP, and unilateral nerve sparing was performed in 6 patients. There were no significant differences in the age, pretreatment serum PSA value, T-stage, or

Table 1. Patient characteristics

Variable		RT-IMRT	RP	*P*-value
Age (years)	median	69	67	0.157
	range	53–79	53–76	
PSA, (ng/ml)	median	7.5	9.1	0.892
	range	4.2–53.1	1.3–46.6	
T-stage (no. of patients)	T1c	16	36	0.761
	T2	5	10	
	T3	2	2	
Gleason score (no. of patients)	6	13	34	0.206
	7	10	12	
	≥ 8	0	2	
D'Amico classification	low	10	22	0.955
	Intermediate	8	17	
	high	5	9	
Follow-up (months)	median	65	73	0.025
	range	19–89	49–92	

D'Amico's risk classification between the RT-IMRT and RP groups. Early termination of post-treatment follow-up (within 5 years) occurred with two patients in the RT-IMRT group (at 19 and 39 months), and two patients in the RP group (at 49 and 54 months). Hormonal treatment was additionally performed within 5 years after treatment in 2 of the 23 patients in the RT-IMRT group and 10 of the 48 patients in the RP group. The 5-year bPFS rates were 90% [95% confidential interval (CI): 78 to 100%] in the RT-IMRT group and 79% (95% CI: 67 to 90%) in the RP group. This difference was not significant (log-rank test: $P = 0.78$). One patient in each group died before the end of the study, but the deaths were not PC-related.

Acute urological complications such as frequent urination, difficulty urinating, and pain on urination were noted in 8 patients (35%) following RT-IMRT. However, the complications observed in these patients were assigned a score of 1 according to the Radiation Therapy Oncology Group (RTOG) Complication Grading [10]. There were no acute gastrointestinal complications reported. Gastrointestinal complications (RTOG Grade 1) without urological complications were observed at later time points in 2 patients (8%).

Compliance with Hr-QOL measures

Over the course of the study, Hr-QOL forms for the RT-IMRT group were received from 23 (100%) patients at the time of treatment, 23 (100%) patients 1 year post-treatment, 21 (91%) patients 3 years post-treatment, and 19 (83%) patients 5 years post-treatment. In the RP group, Hr-QOL forms were received from 48 (100%) patients at the time of treatment, 47 (98%) patients 1 year post-treatment, 45 (94%) patients 3 years post-treatment, and 42 (88%) 5 years post-treatment.

Comparison of Hr-QOL

Hr-QOL was compared using the SF-36 questionnaire (Table 2). There were no significant differences between the RT-IMRT and RP groups in any parameter at the time of treatment (baseline). There were no significant differences between the two groups at 1, 3 or 5 years after treatment. There were also no significant differences in QOL between both treatment groups and the Japanese population. Lastly we examined changes in QOL within the RT-IMRT and RP groups and found no significant changes between QOL values between baseline and 1, 3 or 5 years post-treatment in either group.

Comparison of disease-specific QOL

Parameters of the disease-specific QOL were evaluated. These included urinary function and bother, bowel function and bother, and sexual function and bother measurements (Table 3). In the baseline assessments, there were no significant differences for any parameter between the RT-IMRT and RP groups. Urinary function scores at 1, 3 and 5 years post-treatment were significantly better in the RT-IMRT group compared to the RP group. Looking at changes in urinary function in the RP group over time revealed significantly lower scores at 1, 3 and 5 years after treatment compared to the baseline value for this group. In the RT-IMRT group however, urinary function was not significantly altered at any time post-treatment compared to the baseline. There were no significant differences in the urinary bother score between the two groups at any point, nor were there any differences within each group over time. No significant differences in the bowel function or bowel bother scores were detected between the two groups at any time-point, nor were there any changes within each group over time.

Table 2. SF-36 scores of patients who underwent RT-IMRT and RP

		Baseline	1 year	3 year	5 year	Serial Comparison (*P*-value)
PF-N	RT-IMRT	47 ± 12	48 ± 13	44 ± 15	42 ± 16	0.534
	RP	49 ± 10	50 ± 12	48 ± 13	46 ± 16	0.433
	RT-IMRT vs RP (*P*-value)	0.466	0.385	0.323	0.294	
RP-N	RT-IMRT	48 ± 10	48 ± 11	45 ± 12	45 ± 12	0.746
	RP	47 ± 13	49 ± 14	47 ± 14	44 ± 16	0.349
	RT-IMRT vs RP (*P*-value)	0.765	0.418	0.511	0.918	
BP-N	RT-IMRT	53 ± 11	54 ± 10	52 ± 10	50 ± 12	0.661
	RP	52 ±10	56 ± 7	56 ± 9	54 ± 9	0.116
	RT-IMRT vs RP (*P*-value)	0.566	0.623	0.088	0.214	
GH-N	RT-IMRT	47 ± 10	47 ± 10	48 ± 10	47 ± 9	0.93
	RP	49 ± 10	49 ± 11	49 ± 11	47 ± 11	0.801
	RT-IMRT vs RP (*P*-value)	0.817	0.281	0.925	0.919	
VT-N	RT-IMRT	52 ± 9	54 ± 9	52 ±11	51 ± 10	0.82
	RP	54 ± 10	55 ± 9	55 ± 11	54 ± 11	0.85
	RT-IMRT vs RP (*P*-value)	0.354	0.488	0.237	0.377	
SF-N	RT-IMRT	48 ± 9	52 ± 10	49 ± 11	48 ± 12	0.605
	RP	48 ± 12	52 ± 10	50 ± 10	48 ± 12	0.177
	RT-IMRT vs RP (*P*-value)	0.701	0.769	0.529	0.989	
RE-N	RT-IMRT	51 ± 8	50 ± 11	47 ± 11	46 ± 12	0.532
	RP	49 ± 12	50 ± 13	48 ± 13	46 ± 15	0.464
	RT-IMRT vs RP (*P*-value)	0.946	0.896	0.751	0.949	
MH-N	RT-IMRT	49 ± 9	54 ± 9	54 ± 9	52 ± 10	0.291
	RP	49 ± 10	53 ± 10	53 ± 10	52 ± 11	0.128
	RT-IMRT vs RP (*P*-value)	0.915	0.745	0.974	0.767	

Serial comparisons were using repeated measures ANOVA followed by Dunnett's multiple comparison test. *$P < 0.05$ compared to baseline values. PF = physical functioning, RP = role limitations due to physical health, BP = bodily pain, GH = general health perceptions, VT = vitality, SF = social functioning, RE = role limitations due to emotional problems, MH = mental health, -N = normal-based score.

The sexual function scores prior to treatment were low in both the RT-IMRT group (37 ± 27) and the RP group (45 ± 23). Sexual function scores were significantly higher in the RT-IMRT group compared to the RP group at 1, 3 and 5 years after treatment. Sexual function scores in the RP group were significantly lower at 1, 3 and 5 years after treatment compared with their baseline values. In the RT-IMRT group, however, no significant changes from the baseline value were observed at any point. Sexual function was markedly affected for some patients in both groups prior to treatment, which may confound interpretation of the results. Therefore, we analyzed 12 patients in the RT-IMRT group who had a baseline score of ≥ 40 and 13 patients in the RP group for whom bilateral nerve preservation was performed (Fig. 1). Among these subjects, the sexual function scores were significantly higher in the RT-IMRT group at 1, 3 and 5 years after treatment compared to the RP group. Sexual bother scores did not differ between the two groups at any time-point, nor did they change over time within either group.

Comparison of anxiety/depression

Mental stress after treatment was evaluated using the HAD scale (Table 4). No significant changes within each group over time or differences between the two groups were observed at any time-point.

DISCUSSION

This study demonstrated that RT-IMRT better preserved urinary and sexual functions over long periods of time than did RP. We also report no significant differences in bowel function and bother, which is frequently worsened by radiotherapy, between the two procedures. Furthermore, there was no significant difference in bPFS between the two groups.

Many studies have examined QOL after external radiation therapy for localized PC and a few comparative studies have investigated Hr-QOL after RP [11, 12]. However, most studies have compared RP with classical radiation therapy.

Table 3. CLA-PCI scores of patients who underwent RT-IMRT and RP

		Baseline	1 year	3 year	5 year	Serial Comparison (*P*-value)
UF	RT-IMRT	87 ± 16	93 ± 13	94 ± 12	90 ± 13	0.309
	RP	86 ± 18	72 ± 27*	73 ± 28*	72 ± 26*	0.024
	RT-IMRT vs RP (*P*-value)	0.746	0.001	0.001	0.003	
UB	RT-IMRT	88 ± 19	90 ± 17	86 ± 22	89 ± 20	0.866
	RP	84 ± 21	85 ± 26	83 ± 24	86 ± 24	0.927
	RT-IMRT vs RP (*P*-value)	0.589	0.604	0.651	0.647	
BF	RT-IMRT	84 ± 13	89 ± 12	89 ± 13	83 ± 18	0.392
	RP	88 ± 15	87 ± 14	88 ± 13	86 ± 15	0.831
	RT-IMRT vs RP (*P*-value)	0.175	0.69	0.824	0.721	
BB	RT-IMRT	88 ± 19	89 ± 18	86 ± 21	83 ± 24	0.817
	RP	90 ± 20	92 ± 20	90 ± 19	85 ± 23	0.398
	RT-IMRT vs RP (*P*-value)	0.381	0.247	0.442	0.751	
SF	RT-IMRT	37 ± 27	35 ± 25	33 ± 23	29 ± 24	0.718
	RP	45 ± 23	14 ± 18*	15 ± 19*	14 ± 19*	<0.001
	RT-IMRT vs RP (*P*-value)	0.123	0.001	0.006	0.018	
SB	RT-IMRT	73 ± 29	80 ± 21	77 ± 23	78 ± 21	0.792
	RP	76 ± 27	67 ± 26	64 ± 34	65 ± 33	0.223
	RT-IMRT vs RP (*P*-value)	0.738	0.069	0.151	0.144	

Serial comparisons were using repeated measures ANOVA followed by Dunnett's multiple comparison test. *$P < 0.05$ compared to baseline values. UF = urinary function, UB = urinary bother, BF = bowel function, BB = bowel bother, SF = sexual function, SB = sexual bother.

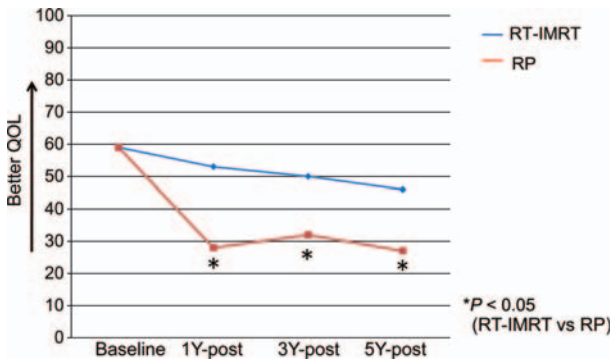

Fig. 1. Serial changes in the sexual function of 12 patients with a baseline score of 40 or higher in the RT-IMRT group and 13 patients in the RP group for whom bilateral nerve preservation was performed. *$P < 0.05$, (RT-IMRT vs RP).

This study represents the first longitudinal study to compare high-accuracy image-guided IMRT with RP over 5 years.

Analyzing QOL after treatment for localized PC presents several issues. The first is whether the QOL was evaluated using an accurate survey method. We employed the most common questionnaire to assess the global QOL, the SF-36 [7]. Using the SF-36 allows results to be compared to the QOL of the general population by converting scores to the NBS. We found no significant differences in QOL between the NBS and either treatment group at any time in the study.

For the disease-specific QOL assessment, the UCLA-PCI was used [8]. Many recent studies use the Expanded Prostate Cancer Index Composite (EPIC) [13], but we were unable to use the EPIC at the beginning of this study. Namiki *et al.* analyzed correlations between the UCLA-PCI and the EPIC and found strong correlations between the two surveys for urinary and sexual function, but only a weak correlation for bowel function [14]. However, they indicate studies using the UCLA-PCI did not markedly differ from those using the EPIC.

There was no difference between the groups with respect to the Hr-QOL before the start of treatment. Chen *et al.* evaluated QOL in 409 patients and reported that the pretreatment QOL markedly influenced the post-treatment QOL [15]. The patient background factors, Hr-QOL, disease-specific QOL, and mental stress were similar in the RT-IMRT and RP groups and although this was not a randomized study, patient groups were well balanced regarding background.

It is also important to examine whether the post-treatment QOL in the RP group, which served as the control group in our study, is similar to that previously reported. Namiki *et al.* used the UCLA-PCI to longitudinally evaluate the disease-specific QOL over 5 years in 154 patients who underwent RP [16]. They found scores in all domains of UCLA-PCI were nearly identical to those of the 48 patients we investigated. Results reported by Hashine *et al.* [17] were also consistent with our findings in the RP group. Furthermore,

Table 4. HAD scores of patients who underwent RT-IMRT and RP

		Baseline	1 year	3 year	5 year	Serial Comparison (*P*-value)
Anxiety	RT-IMRT	4.3 ± 2.5	3.0 ± 2.5	3.7 ± 2.6	3.4 ± 2.9	0.464
	RP	5.1 ± 3.8	3.6 ± 3.8	3.8 ± 4.2	3.8 ± 3.8	0.213
	RT-IMRT vs RP (*P*-value)	0.438	0.947	0.413	0.953	
Depression	RT-IMRT	4.9 ± 3.3	3.7 ± 2.7	4.6 ± 3.8	4.4 ± 3.6	0.675
	RP	4.5 ± 3.8	3.6 ± 4.1	3.7 ± 4.1	4.3 ± 4.0	0.585
	RT-IMRT vs RP (*P*-value)	0.639	0.273	0.299	0.722	

Serial comparisons were using repeated measures ANOVA followed by Dunnett's multiple comparison test. $*P < 0.05$ compared to baseline values.

post-operative sexual function in patients who underwent nerve-sparing RP could affect outcomes in our study. Gacci *et al.* recently reported long-term urinary and sexual outcomes in patients receiving RP who remained disease-free [18]. They reported a mean sexual function score of 34 on the UCLA-PCI at 5 years post-surgery in 125 patients with nerve-sparing RP. This is similar to the mean sexual function score (28) at 5 years post-treatment in our patients who underwent nerve-sparing RP (Fig. 1).

We reviewed the post-treatment QOL in the RT-IMRT group and found the global QOL did not change in the RT-IMRT group over time and was also similar to the RP group at each time-point. Lips *et al.* used the SF-36 to investigate the global QOL up to 3 years after IMRT at 76 Gy, and found that the emotional role restriction and mental health scores significantly improved from baseline values, but physical function scores were significantly reduced [19]. Marchand *et al.* prospectively examined the post-treatment global QOL in the IMRT-treated group 18 months after treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30). They found no significant changes in any domain of the global QOL compared to baseline values [20]. Namiki *et al.* used the SF-36 to investigate changes in the global QOL over 5 years in 36 patients who underwent IMRT [21]. There were no significant changes in any domain value of SF-36 compared to baseline values, which is consistent with our findings that RT-IMRT did not reduce the global QOL.

Marchand *et al.* reported on disease-specific QOL for patients who underwent IMRT using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate-specific 25-item (EORTC-QLQ PR25). At 18 months post-treatment, they found no differences in urinary symptoms/problems, bowel symptoms/problems, sexual function or activity compared to pre-treatment [20]. Lips *et al.* reported however, that sexual activity was significantly reduced 3 years after treatment using a similar QOL survey method [19]. Namiki *et al.* examined the disease-specific QOL using the UCLA-PCI and found that the sexual function deteriorated 5 years after treatment [21]. In our study, there were no marked changes in urinary, bowel or sexual function following RT-IMRT. This could be due to the increased accuracy of RT-IMRT, which left the lateral prostatic neuro-vascular bundle undisturbed.

Mental stress is another important factor concerning cancer treatment. Even patients with early PC may become anxious or depressed [19]. Our study showed that over the 5-year period, there was no change in anxiety or depression compared with the baseline levels in patients who received RT-IMRT. Furthermore, there were no significant differences between RT-IMRT and RP at any evaluation point. Considering this, RT-IMRT may minimally perturb the emotional status of patients for long periods.

RT-IMRT did not cause measureable deterioration of the global QOL, disease-specific QOL, or emotional status of patients. We show that the pretreatment QOL could be maintained for a long periods suggesting that this procedure may be more appropriate than RP. This study has limitations and warrants further investigation. First, this was not a randomized study. We do show however, there were no differences in patient backgrounds and the pretreatment values of each QOL score between the RT-IMRT and RP groups. The first author (NS) is an urologist rather than a radiation oncologist. These factors could minimize the selection bias and publication bias. The second limitation is the small number of patients used in this study. A study of larger numbers of patients is warranted to fully understand the effects of RT-IMRT on QOL. In summary, the present study suggests that RT-IMRT is an appropriate treatment for localized PC given its similar efficacy compared with RP and the relatively greater preservation of post-treatment QOL.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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