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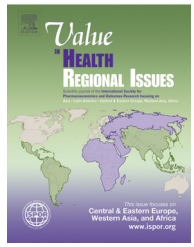

Conventionally Fractionationed Volumetric Arc Therapy versus Hypofractionated Stereotactic Body Radiotherapy: Quality of Life, Side Effects, and Prostate-Specific Antigen Kinetics in Localized Prostate Cancer

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ABSTRACT

Objectives: To compare conventionally fractionationed volumetric arc therapy (VMAT) and hypofractionated stereotactic body radiotherapy (SBRT) modalities in terms of prostate-specific antigen (PSA) kinetics, toxicity, and quality of life (QOL) in patients with localized prostate cancer. **Methods:** Patients received radical radiotherapy as either 33.5 Gy/5 fr for SBRT or 75.6 Gy/35 fr for VMAT. International Prostate Symptom Score (IPSS) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module (QLQ-PR25) forms were used to assess QOL. **Results:** Of the 48 patients (28 in SBRT and 20 in VMAT) included in the study, 40 (20 in SBRT and 20 in VMAT) were evaluated for QOL status. PSA control rate was 100% and PSA nadir value was 0.5 ng/dl in both arms during the median follow-up period of 23 months. The magnitude of PSA bounce was higher in the SBRT arm than in the VMAT arm ($P = 0.01$). The PSA decline rate in the VMAT arm was higher than in the SBRT arm ($P = 0.028$). Three (10.7%) patients treated with SBRT who had a history of transurethral resection of the prostate (TURP) experienced grade 3 urinary toxicity. No significant difference was observed concerning sexual activity and sexual functioning scores, whereas scores at 10.5 and 13.5 months were decreased in both arms. The SBRT and VMAT arms had similar urinary incontinence, bowel symptoms, and IPSS obstruction scores. The magnitude of increase in IPSS scores at treatment completion was higher in the VMAT arm than in the SBRT arm ($P = 0.046$). The decrease in hormonal symptom scores at 4.5, 10.5, and 13.5 months was higher in the VMAT arm than in the SBRT arm ($P = 0.007$, 0.027, and 0.021, respectively). **Conclusions:** Both treatment modalities had similar effectiveness and provided acceptable outcomes in terms of toxicity and QOL. Grade 3 urinary toxicities might be eliminated with careful patient selection for SBRT.

Keywords: prostate cancer, quality of life, SBRT, toxicity, VMAT.

Introduction

Prostate cancer is the most common type of cancer in men. In 2014, some 233,000 patients were newly diagnosed as having prostate cancer, which constitutes 27% of new cancer cases in men [1]. Nevertheless, deaths due to prostate cancer were reduced by 4.1% per year between 1994 and 2001; 29,480 deaths occurred because of prostate cancer in 2014 [1]. This low mortality rate can be explained by the awareness of early detection in the community and increased disease control through effective treatment modalities. Nevertheless, early diagnosis and treatment of prostate cancer that does not threaten life expectancy may result in unnecessary adverse effects, deterioration in quality of life (QOL), and an increase in health care costs. Thus, the determination of treatment indication and treatment modalities to be applied is one of the most important issues in prostate cancer management.

There are many different options for the treatment of localized prostate cancer, including active surveillance, surgery, brachytherapy, cryotherapy, and high-intensity focused ultrasound, but each has its unique adverse effects. External beam radiotherapy (RT) is another treatment modality that increased biochemical control rates in patients with prostate cancer [2,3]. The results of dose escalation studies in the 1990s revealed that increased RT doses led to higher prostate-specific antigen (PSA) control rates, as well as increased toxicity, mainly in the form of rectal bleeding [2–4].

The therapeutic index has increased considerably through the ability of highly conformal dose constraints for normal tissue provided by modern technology. Intensity-modulated radiation

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therapy (IMRT) led to decreased toxicity rates while increasing local control rates [5,6]. In addition, volumetric arc therapy (VMAT) was shown to provide better outcomes than other IMRT techniques in terms of target organ coverage, conformity index, homogeneity index, the dose received by organs at risk, monitor unit (MU) delivered, and acute toxicities in many dosimetric studies [7–9]. Therefore, the use of VMAT has become widespread instead of other IMRT techniques in centers with available infrastructure for the arc therapy.

The therapeutic index is theoretically expected to be increased with hypofractionated regimens because the α/β ratio of prostate cancer cells is approximately 1.5. On the basis of this hypothesis, many studies were conducted that investigated the efficacy of the linear accelerator–based or robotic-based stereotactic body radiotherapy (SBRT). The results of these studies involving 1100 patients with localized prostate cancer who received a median dose of 36.25 Gy (range, 35–40 Gy)/4 to 5 fr for noncoplanar robotic SBRT were reported in the SBRT consortium. Five-year biochemical relapse-free survivals for low-, medium-, and high-risk patients were detected as 95%, 84%, and 81%, respectively [10].

Both SBRT and VMAT treatments have unique theoretical advantages. Nevertheless, a much shorter total treatment time in SBRT treatment compared with VMAT treatment is one of the greatest advantages of SBRT for treatment centers and patients. Although the efficacy of both treatments was illustrated in several studies, the follow-up period of SBRT treatment is not as long as that of fractionationed regimens, which makes long-term follow-up periods important regarding adverse effects [10].

Nowadays, the satisfaction and QOL of patients have become as important as the success of treatment. Treatment toxicity and QOL of patients are decisive factors in choosing the treatment modality to be administered among different treatment options for prostate cancer, which has a high control ratio and long survival expectancy. Therefore, for the first time in the literature, we intended to compare conventionally fractionationed VMAT with hypofractionated SBRT in terms of PSA kinetics, treatment-related adverse effects, and QOL inpatients with localized prostate cancer.

Methods

Patients diagnosed with localized prostate cancer who were admitted to our institution between March 2010 and December 2013 and met the study criteria were included in this prospective study. The terms of the study were approved by the institutional ethics committee. Procedures were conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2000. The informed consent from patients was taken before treatment.

Forty-eight patients were included in the study (28 in SBRT and 20 in VMAT). In addition, of these 48 patients, 40 (20 in SBRT and 20 in VMAT) were evaluated for their QOL status with appropriate forms and questionnaires. The remaining 8 patients in the SBRT arm were excluded from the QOL assessment because of incompliance while responding to the questions in the QOL forms.

Androgen deprivation therapy (ADT) was administered as a monotherapy including bicalutamide 50 mg (1×1) for 10 days followed by leuprolide acetate at 3-month intervals. RT treatment planning was scheduled after 3 months following ADT initiation. Two weeks before RT simulation, three to four gold fiducial markers were inserted transrectally by an experienced radiologist. The fiducials were placed in the apex, lateral zone, and base of the prostate. Contrast-enhanced planning computed tomography with 1-mm slice thickness was done using the Philips Brilliance (Philips Switzerland, Amsterdam, the Netherlands) device.

RT Treatment Planning

The prostate gland, seminal vesicles, rectum, bladder, penile bulb, femoral heads, and fiducials were contoured. A clinical target volume (CTV) was created with no margin to the prostate and in very low risk and low-risk patients, whereas the CTV included the prostate and the 1-cm proximal part of the vesicula seminalis in other patients without margin. A 3-mm margin posteriorly and a 5-mm margin from other directions were given to the CTV to create a planning target volume. Conturing was performed using a Varian Eclipse TPS version 8.9 (Varian Medical Systems, Palo Alto, CA) planning system for VMAT planning. Double full arcs with 179.9 to 180.1 gantry angles counterclockwise and 180.1 to 179.9 gantry angles clockwise were planned using 6-MV photon energy. RT was performed using a Varian DHX RapidArc (Varian Medical Systems, Palo Alto, CA) device. Delineation was performed using the MultiPlan MD Suite planning system (Accuray, Sunnyvale, CA, USA) for SBRT planning. RT was administered with a (Accuray, Sunnyvale, CA, USA) device to patients in the SBRT arm. Patients received radical RT with dose schedules of either 33.5 Gy/5 fr for SBRT or 75.6 Gy/35 fr for VMAT, the biological 2-Gy equivalent dose for both of which was 78 Gy/39 fr.

RT Toxicity Assessments

Acute and late toxicity of RT were evaluated on the basis of Common Terminology Criteria for Adverse Events version 4.

QOL Assessments

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Prostate Cancer Module (QLQ-PR25) module questionnaire and the International Prostate Symptom Score (IPSS) form were used to assess the QOL of patients before and at the end of treatment, 1.5 months post-treatment, and during subsequent control periods at 3-month intervals. The EORTC QLQ-PR25 module consists of parameters to evaluate the functionality and symptoms of patients. All scales were scored from 0 to 100. Higher scale scores indicate a greater level of response. Higher scores for functioning scales show higher/healthier levels of functionality, but higher symptom scale scores indicate greater symptoms/problems [11].

The IPSS comprises eight questions (seven symptom questions and one QOL question) to screen symptoms of the lower genitourinary track. The seven symptom questions are related to the following: 1) feeling of incomplete bladder emptying, 2) frequency, 3) intermittency, 4) urgency, 5) weak stream, 6) straining, and 7) nocturia. Each could be scored from 1 to 5 for a maximum of 35 points. The eighth question on QOL is assigned a score of 1 to 6. The IPSS obstruction (IPSS-O) score is the sum of IPSS questions 1, 3, 5, and 6, which show the degree of symptoms related to the obstruction of the urinary tract.

The QOL measures were recorded face to face before seeing the physician, and the same order was followed each time. Figure 1 shows the medical interventions and the timing of the administration of QOL assessments.

Statistical Analysis

For descriptive statistics of the data, mean, SD, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was measured using the Kolmogorov-Smirnov test. The independent samples t test and the Mann-Whitney U test were used for the analysis of quantitative data. The paired Wilcoxon test was used to analyze repeated