Clinical Oncology xxx (2016) 1–6

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

High-quality Linac-based Stereotactic Body Radiation Therapy with Flattening Filter Free Beams and Volumetric Modulated Arc Therapy for Low–Intermediate Risk Prostate Cancer. A Mono-institutional Experience with 90 Patients

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Received 23 January 2016; received in revised form 30 May 2016; accepted 1 June 2016

Abstract

Aims: The aim of this phase II study was to evaluate the efficacy and toxicity of stereotactic body radiotherapy in patients with low or intermediate risk prostate cancer.

Materials and methods: Biopsy-confirmed prostate cancer patients were enrolled, provided that they had the following characteristics: initial prostate-specific antigen (PSA) $\leq$ 20 ng/ml, Gleason Score $\leq$ 7, International Prostate Symptom Score $\leq$ 7. The treatment schedule was 35 Gy in five fractions, delivered with volumetric modulated arcs with flattening filter free beams. Toxicity was recorded according to CTCAE criteria v4.0. Biochemical failure was calculated according to the Phoenix definition. The Expanded Prostate Cancer Index Composite questionnaire was used to record health-related quality of life.

Results: Between December 2011 and March 2015, 90 patients were enrolled (53 low risk, 37 intermediate risk). The median age was 71 years (range 48–82). In total, 58 (64.5%) of the patients had Gleason Score = 6, the remaining had Gleason Score = 7. The median initial PSA was 6.9 ng/ml (range 2.7–17.0). Acute toxicity was mild, with 32.2 patients presenting grade 1 urinary toxicity and 32.2% of patients presenting grade 2 urinary toxicity, mainly represented by urgency, dysuria and stranguria. Rectal grade 1 toxicity was found in 15.5% of patients, whereas grade 2 toxicity was recorded in 6.6% of patients. Regarding late toxicity, grade 1 proctitis was recorded in 11.1% of patients and grade 1 urinary in 38.8%; only two events of grade 2 urinary toxicity were observed (transient urethral stenosis, resolved by a 24 h catheterisation). At a median follow-up of 27 months (6–62 months) only two intermediate risk patients experienced a biochemical failure. Health-related quality of life revealed a slight worsening in all the domains during treatment, with a return to baseline 3 months after treatment.

Conclusions: Stereotactic body radiotherapy delivered using linac-based flattening filter free volumetric modulated arc radiotherapy in low and intermediate risk prostate cancer patients is associated with mild toxicity profiles and good patient-reported quality of life.

Key words: Flattening filter free beams; hypofractionation; prostate cancer; RapidArc; SBRT

Introduction

Prostate cancer is among the most common neoplasms among men and one of the leading causes of death [1].

Radical surgery and radiotherapy are considered the treatments of choice in cases of localised or locally advanced disease, yet being burdened, at times, by significant effects, especially regarding the genitourinary and sexual spheres [2].

The sharp rise in early diagnosis through screening with prostate-specific antigen (PSA), the improvement in diagnostic techniques for proper staging, the evolution of surgical techniques and radiotherapy, as well as the

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http://dx.doi.org/10.1016/j.clon.2016.06.013
0936-6555/

introduction of new drugs in the clinical practice, contributed to the improvement in prognosis as well as to the quality of life for these patients [3]. Survival studies have shown that for prostate cancer patients with a Gleason Score below 7 and a PSA lower than 10 ng/ml, an active treatment could be unnecessary [4,5].

The issue of hypofractionation and stereotactic body radiotherapy (SBRT) for prostate cancer is relevant, especially for those patients with localised prostate cancer who do not meet the criteria of the so-called low risk disease, having a Gleason Score of 7 and/or a PSA of 10–20 ng/ml (intermediate risk disease) or those who refuse/fail the active surveillance protocols.

For these patients, a standard fractionation treatment over 7–8 weeks or radical prostatectomy could seem overwhelming [6]. Several studies argue for a low alpha/beta ratio for prostate cancer, even lower than the value of 3. Given this theory, the potential exists for hypofractionation to significantly improve the therapeutic ratio [7].

Several studies suggested a clinical confirmation of this hypothesis, showing comparable results to standard fractionation by delivering only four or five high dose fractions [8].

On the basis of this evidence, we designed a study of SBRT for early stage prostate cancer. The schedule was 35 Gy in five fractions, delivered every other day with a volumetric modulated arc therapy and flattening filter free technology. The aim of the study was to verify the safety and efficacy of this treatment.

Materials and Methods

This prospective phase II study was approved by the ethics committee of our institute in 2012. The study design was already described in a preliminary report [9].

Patient Selection

Patients with histologically proven prostate cancer were enrolled into this study, provided that they had low or intermediate risk disease according to the National Comprehensive Cancer Network criteria [10].

Further inclusion criteria were: age $\leq$ 80 years; World Health Organization performance status $\leq$ 2; PSA level $\leq$ 20 ng/ml; T1–T2 stage; no pathological lymph nodes on computed tomography/magnetic resonance imaging scans; no distant metastases; no previous prostate surgery other than transurethral radical prostatectomy (TURP) (at least 6 weeks before the start of radiotherapy); no malignant tumours in the previous 5 years; International Prostate Symptom Score in the range 0–7; written informed consent.

Exclusion criteria were: clinical positive pelvic lymph nodes or risk of nodal metastases >15% according to the Roach formula; previous TURP less than 6 weeks before radiotherapy; previous prostate surgery other than TURP; previous pelvic irradiation; inability to obtain written informed consent. Combined androgen deprivation therapy (ADT) was not prescribed, but was maintained for 6 months in patients who had already been prescribed ADT by the urologist or the family doctor.

Stereotactic Body Radiotherapy Treatment Details

The chosen treatment schedule was 35 Gy in five fractions, corresponding to a 2 Gy equivalent dose of 70–85 Gy for an alpha/beta estimate between 3 and 1.5 Gy. Treatment was administered on alternate days.

Patients were requested to present with a full bladder and an empty rectum, both for planning and for daily treatments. A urinary catheter was positioned only for simulation purposes to better identify the urethra and the bladder was filled with 200 cm^3 of 0.9% NaCl solution and then removed after simulation computed tomography. Target definition was based on computed tomography with the support of contrast magnetic resonance imaging for a better definition of anatomical relationships between prostate and surrounding organs at risk (rectum, bladder and penile bulb) and to define urethra position. The clinical target volume (CTV) was considered the prostate plus entire seminal vesicles in patients with intermediate risk disease, whereas for patients with low risk disease, the CTV was represented by the prostate only. The planning target volume (PTV) was defined isotropically expanding the CTV by 5 mm as standard, reduced to 3 mm in the case of conflict with organs at risk (rectum).

Dose-volume constraints for normal tissues had priority over the PTV in cases of overlap. Target coverage was required to be: $V_{95\%} > 99\%$ on CTV (95% on PTV). Dose-volume objectives for organs at risk (OAR) were (in brackets the mandatory minimum values): for rectum $V_{18Gy} < 35\%$; $V_{28Gy} < 10\%$ (15%); $V_{32Gy} < 5\%$ (10%); $D_{1\%} < 35$ Gy; for bladder $D_{1\%} < 35$ Gy. For the urethra, no planning risk volume was defined around it but, due to the presence of the catheter, optimisation was driven to avoid foci of dose higher than 100% of the prescription in that area. For other organs (femoral heads, penis bulb and healthy tissue), the planning strategy was to minimise the involvement as much as possible.

Treatment plans were designed and optimised according to the RapidArc technique, with one or two full arcs. All plans were optimised and delivered on a TrueBeam linac (Varian Medical Systems, Palo Alto, CA, USA), choosing 10 MV flattening filter free photon beams. In the case of metal implants in the femoral heads of patients, avoidance sectors were allowed to exclude direct entrance of photon beams. Treatment delivery was image guided. Before each radiation fraction delivery, cone beam computed tomography (CBCT) was carried out to verify the correct position and requested conditions (full bladder, empty rectum). Couch repositioning, when necessary, was carried out after automatic matching of CBCT images to reference planning computed tomography. The protocol study suggests the use of fiducial markers for CBCT guidance to reduce set-up errors and these were used to compute the eventual positioning shifts by comparing planning computed tomography and CBCT. As the use of fiducial markers was not a mandatory

Please cite this article in press as: D'Agostino G, et al., High-quality Linac-based Stereotactic Body Radiation Therapy with Flattening Filter Free Beams and Volumetric Modulated Arc Therapy for Low–Intermediate Risk Prostate Cancer. A Mono-institutional Experience with 90 Patients, Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.06.013