Original Research Article

The effect of prostate motion during hypofractionated radiotherapy can be reduced by using flattening filter free beams

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ABSTRACT

Background and purpose: Hypofractionated radiotherapy of prostate cancer reduces the overall treatment time but increases the per-fraction beam-on time due to the higher fraction doses. This increased fraction treatment time results in a larger uncertainty of the prostate position. The purpose of this study was to investigate the effect of prostate motion during flattening filter free (FFF) Volumetric Modulated Arc Therapy (VMAT) in ultra-hypofractionation of prostate cancer radiotherapy with preserved plan quality compared to conventional flattened beams.
Materials and methods: Nine prostate patients from the Scandinavian HYPO-RT-PC trial were re-planned using VMAT technique with both conventional and flattening filter free beams. Two fractionation schedules were used, one hypofractionated (42.7 Gy in 7 fractions), and one conventional (78.0 Gy in 39 fractions). Pre-treatment verification measurements were performed on all plans and the treatment time was recorded. Measurements with simulated prostate motion were performed for the plans with the longest treatment times.
Results: All the 10FFF plans fulfilled the clinical gamma pass rate, 90% (3%, 2 mm), during all simulated prostate motion trajectories. The 10MV plans only fulfilled the clinical pass rate for three of the trajectories. The mean beam-on-time for the hypofractionated plans were reduced from 2.3 min to 1.0 min when using 10FFF compared to 10MV. No clinically relevant differences in dose distribution were identified when comparing the plans with different beam qualities.
Conclusion: Flattening-filter free VMAT reduces treatment times, limiting the dosimetric effect of organ motion for ultrahypofractionated prostate cancer with preserved plan quality.

1. Introduction

Prostate cancer is the most common form of cancer among the male population in Europe. A large number of these patients are treated with external beam radiotherapy [1,2]. Treatment with curative intent is conventionally given in 2 Gy fractions to total doses in the range 74–80 Gy to the prostate, i.e. in 37–40 fractions over 7–8 weeks.

The large number of prostate cancer patients and the long treatment courses have raised the demand for more time efficient treatment methods. Over the last couple of years several studies have proposed that the α/β ratio for prostate cancer is low, suggesting a potential benefit for hypofractionation, thus shortening the course of treatment by several weeks [3]. This has recently been confirmed for intermediate risk prostate cancer in a large randomized study comparing moderately hypofractionated treatment regimens (3 Gy/fraction) with conventional

fractionation [4]. Several studies have been set up to explore a more extreme hypofractionation, including a Scandinavian prospective randomized phase III trial (HYPO-RT-PC) [5]. This study compares a total dose of 42.7 Gy in 7 fractions (6.1 Gy/fraction) with 78.0 Gy in 39 fractions (2.0 Gy/fraction) for intermediate risk prostate cancer patients.

In the HYPO-RT-PC study, image guidance prior to every treatment fraction is mandatory. Three gold markers are implanted into the prostate before the CT scanning. Before each fraction, kV-images are taken and the gold markers are matched to the reference image set. The prostate is therefore considered to be in the correct position when every treatment session is started, limited by the uncertainty of the image matching process. Despite this, the prostate position can be affected during the treatment due to rectal activity, bladder filling, muscle clenching and general pelvic motion [6]. Several studies have

investigated this issue, trying to predict the occurrence and extent of the prostate movement [7,8].

Several independent studies, using different methods, have found similar prostate motion trajectories. There are six different prostate motion patterns described [9–13]. The pattern of an individual patient is unpredictable and any of the six motion patterns can occur during each fraction. In any case, the positional uncertainty increases with time [12–16]. The increased dose per fraction and thereby increased treatment time for hypofractionation could lead to larger positional uncertainty due to the prostate motion. Flattening filter free (FFF) beams, which have higher dose rates, might offer a solution in decreasing the treatment time per fraction for ultrahypofractionation of prostate cancer. A number of planning studies have investigated the plan quality and treatment time of FFF beams for hypofractionation of prostate cancer [17–21]. Most of them have shown a decreased treatment time for FFF beams with preserved plan quality for hypofractionation but no time saving for conventional fractionation. Some of the studies perform a pre-treatment QA measurement to ensure the deliverability of the treatment plans. To our knowledge, no study has investigated the potential reduction in prostate motion effects during beam delivery due to the shorter treatment times.

The aim of this study was to investigate the effects of intrafractional prostate motion using ultrahypofractionated treatments of prostate cancer with FFF beams.

2. Materials and methods

Nine prostate cancer patients from the HYPO-RT-PC trial were selected for the study. The patients were chosen based on prostate size ("small", "medium" and "large") in order to explore the difference in treatment delivery for different target volumes. Three patients were chosen at random from each size category. Five of the patients were originally treated in the conventional arm of the HYPO-RT-PC study and four in the hypofractionated arm. The CTV was defined as the prostate as seen on the CT with MRI guidance as stated in the trial protocol. The PTV was generated from the CTV with a 7-mm isotropic margin added. All selected patients were treated with a VMAT technique. This study was approved by the Regional Ethics Board of Lund, Sweden (EPN Lund, Dnr 2013/742)

Six VMAT plans were optimised for each patient. The original patient treatment plans were not used in this study. Three different beam qualities were studied, 10MV flattened beam (10MV), 6MV flattening filter free (6FFF) and 10MV flattening filter free (10FFF). Two plans were generated for each energy; one with the conventional fractionation (78 Gy in 39 fractions), and one with hypofractionation (42.7 Gy in 7 fractions). Optimisation objectives were individually set for each plan and beam quality to fulfil the dose constraints defined in the HYPO-RT-PC study protocol. To obtain optimal plans, the study protocols prioritised clinical objective list was used. The plans were considered optimal when a lower priority objective could not be improved without deteriorate a higher prioritised objective. All treatment plan optimisation was made in the Eclipse Treatment Planning system (TPS) version 13 (Varian Medical Systems). The dose calculation algorithm used was the Analytical Anisotropic Algorithm (AAA) version 10.0.28. All plans were made with a single 360° arc VMAT. A maximum dose rate was allowed for each beam quality; 600 MU/min for 10MV, 1400 MU/min for 6FFF and 2400 MU/min for 10FFF. The final plans were reviewed and approved as clinically acceptable by a senior radiation oncologist.

A pre-treatment verification measurement was performed for all treatment plans according to the clinical routine at the radiotherapy department in Lund. The measurement device used was the Delta^4 phantom (ScandiDos, Uppsala, Sweden). The verification plans were delivered on a Varian TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, USA). The measured and planned doses were compared using a global gamma evaluation [22]. The criteria for the gamma evaluation were (3%, 2 mm), (2%, 2 mm), (2%, 1 mm), and (1%, 1 mm), with a dose threshold of 15%.

During the verification measurements, the beam-on times were recorded from the verification system. The beam-on times were later compared for the different beam qualities.

Dose-volume parameters stated in the trial protocol were extracted to evaluate the treatment plan quality. The median and range of the DVH parameters were calculated for both treatment fractionation arms. The dose parameters were normalised to the prescribed target dose, 78.0 Gy for the conventional arm and 42.7 Gy for the hypofractionated arm. Both the homogeneity index (*HI*) and the conformity index (*CI*) were calculated to further explore and compare the quality of the different treatment plans [23,24]. HI and CI are described in the Supplementary text.

The impact of the intrafractional prostate motion was investigated for the patients with the longest treatment times. To simulate the motion, the Delta^4 Phantom was mounted on the Hexamotion module (ScandiDos, Uppsala, Sweden). The motion data used consisted of six different motion patterns, (stable trajectory, continuous drift, persistent excursion, transient excursion, high-frequency excursions and erratic behaviour), derived from real patient prostate motions by Ng et al. [12]. The motion trajectories were converted with a MatLab (MathWorks, Inc.) program to fit the data format of the Hexamotion's software. The trajectories used can be found in Supplementary figure 1. The selected treatment plans were delivered while the Delta^4 was moved according to the motion patterns. As a reference, the plans were delivered in a static setting with the same origin as defined for the delivery under motion. At the start of each motion pattern, the target was in the correct position to mimic the clinical situation during image-guided radiotherapy. To study the influence of delay, the treatment was started at different times after the start of the motion sequence. For the persistent excursion trajectory the treatment delivery started after 60 s, as an estimated image evaluation time. The transient excursion motion pattern was investigated with different start times for 10MV and 10FFF in order to include the peak offset in both plans. For the 10MV treatment, the beam was started 175 s into the trajectory. The 10FFF plan was started after 200 s.

Since the data did not follow a normal distribution as evaluated by the Kolmogorov-Smirnov test, the Wilcoxon signed rank test was used to evaluate the statistical significance of any differences between the beam qualities. The level of significance was set to $\alpha = 0.05$. The Hodges-Lehmann median differences with 95% confidence intervals were calculated for 10FFF DVH parameters compared to those for 10MV.

3. Results

3.1. Treatment time

The measured beam-on times are presented in Fig. 1 for each combination of beam quality and fractionation scheme. All the conventional plans were delivered within one minute except for the 10MV plan, which was delivered in 1.1 min. The hypofractionated 10MV plans had a mean beam-on time of 2.3 min, ranging from 2.1 to 2.8 min. The hypofractionated flattening-filter free plans had a significantly shorter delivery time. The 6FFF plans had a mean beam-on time of 1.3 min (range: 1.2–1.6 min) and the 10FFF plans had a mean delivery time of 1.01 min (range: 1.00–1.04 min).

3.2. Plan quality

All treatment plans fulfilled the specified dose volume objectives as stated in the trial protocol, see Supplementary table 1. Small, clinically insignificant differences were seen in the DVH parameters for all different beam qualities. A summary of the median of all DVH parameters is presented in Table 1.

Regardless of fractionation scheme or beam quality, no significant