A dosimetric comparison of ultra-hypofractionated passively scattered proton radiotherapy and stereotactic body radiotherapy (SBRT) in the definitive treatment of localized prostate cancer

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ABSTRACT

Background. We compared target and normal tissue dosimetric indices between ultra-hypofractionated passively scattered proton radiotherapy and stereotactic body radiotherapy (SBRT) in the definitive treatment of localized prostate cancer.

Material and methods. Ten patients were treated definitively for localized prostate cancer with SBRT to a dose of 36.25 Gy in 5 fractions prescribed to a volume encompassing the prostate only. Dose-volume constraints were applied to the rectum, bladder, penile bulb, femoral heads, and prostatic and membranous urethra. Three-field passively scattered proton plans were retrospectively generated using target volumes from the same patients. Dosimetric indices were compared between the SBRT and proton plans using the Wilcoxon signed rank test.

Results. All dose constraints were achieved using both ultra-hypofractionated passively scattered proton and SBRT planning. Proton plans demonstrated significant improvement over SBRT in mean dose delivered to the penile bulb (5.2 CGE vs. 11.4 Gy; \( p = 0.002 \)), rectum (6.7 CGE vs. 10.6 Gy; \( p = 0.002 \)), and membranous urethra (32.2 CGE vs. 34.4 Gy; \( p = 0.006 \)) with improved target homogeneity resulting in a significant reduction in hot spots and volumes of tissue exposed to low doses of radiation. Compared to proton planning, SBRT planning resulted in significant improvement in target conformity with a mean index of 1.17 versus 1.72 (\( p = 0.002 \)), resulting in a dose reduction to the volume of bladder receiving more than 90% of the PD (V32.6, 7.5% vs. 15.9%; \( p = 0.01 \)) and mean dose to the left (7.1 Gy vs. 10.4 CGE; \( p = 0.004 \)) and right (4.0 Gy vs. 10.9 CGE; \( p = 0.01 \)) femoral heads.

Conclusion. Target and normal tissue dose constraints for ultra-hypofractionated definitive radiotherapy of localized prostate cancer are readily achieved using both CK SBRT and passively scattered proton-based therapy suggesting feasibility of either modality.

In 2012, more than 1.1 million cases of prostate cancer were diagnosed worldwide with the majority representing early stage clinically localized disease [1,2]. Standard management options for localized disease include active surveillance, surgery, or radiation therapy (RT) with or without androgen deprivation therapy (ADT). Several factors including age, life expectancy, and risk classification play a significant role in the treatment decision making process.

For patients treated with RT, several studies have demonstrated clear benefits to dose escalation in favorable patients with biochemical progression-free survival (BPFS) rates on the order of 80–95% [3–6]. Further utilization of intensity-modulated radiation therapy (IMRT) techniques have allowed for even higher prescribed doses [7,8] with improved BPFS and acceptable rates of treatment-related acute and late toxicities.

Recently, there has been increasing interest in the use of stereotactic body radiotherapy (SBRT) in an effort to increase the biologically effective dose delivered to the prostate without significantly increasing...
late toxicity [9–12]. The rationale for hypofractionated RT in prostate cancer results from several reports that have estimated the $\alpha/\beta$ ratio of prostate cancer cells to be on the order of 1.5 Gy [13–15], thus indicating a greater sensitivity of prostate cancer cells to fraction size as compared to normal late responding tissues with $\alpha/\beta$ ratios of approximately 3–5 Gy. A typical contemporary SBRT prostate treatment plan prescribes a total dose of 36.25 Gy in 5 fractions, thus resulting in a biologically equivalent dose of approximately 90 Gy in 2.0-Gy fractions [9–12,16]. Similar ultra-hypofractionated schedules have been used in high dose rate (HDR) brachytherapy approaches with equivalent outcomes [17]. Results from several ongoing phase II clinical trials employing this approach have reported excellent preliminary clinical outcomes [9–12,16]. The King et al. series has the longest follow-up to date, reporting five-year actuarial BPFS rates of 94%, which compare favorably with contemporary studies of patients treated with conventional IMRT-based approaches [11]. Quality-of-life analyses from several of the phase II clinical trials examining prostate SBRT, including an analysis of patients treated at Georgetown University Hospital (GUH), have demonstrated that prostate SBRT is well tolerated with gastrointestinal (GI) and genitourinary (GU) toxicity rates comparable to conventional fractionated regimens [9–11,16]. Correspondingly, the Radiation Therapy Oncology Group (RTOG) recently opened a phase II randomized trial (0938) comparing quality of life as well as acute and long-term toxicity outcomes in 5- and 12-fraction regimens between different radiation treatment modalities in favorable risk prostate cancer.

Most data regarding ultra-hypofractionated RT in the setting of localized prostate cancer has come from photon-based treatment regimens. Recently, proton-based therapy has emerged as a promising treatment modality based on its theoretically superior normal tissue sparing resulting from the Bragg peak effect. Due to the three-dimensional volume occupied by the tumor, range modulation along the beam path is employed to create a spread-out Bragg peak (SOBP) and cover the planning target volume (PTV). Using a passively scattered SOBP, Mendenhall et al. reported excellent five-year outcome data for prostate cancer patients treated with conventionally fractionated proton therapy [18]. There is, however, very little data existing regarding the use of passively scattered proton therapy in ultra-hypofractionated regimens. In light of this, we performed a dosimetric study to determine the feasibility of using ultra-hypofractionated passively scattered proton therapy in the treatment of localized prostate cancer by comparing target and normal tissue dosimetric indices with CyberKnife (CK)-based SBRT (Accuray Inc., Sunnyvale, CA, USA).

Methods

Treatment planning

Ten consecutive patients with localized prostate cancer were treated definitively at Georgetown University Hospital (Washington, DC) using the optimized CK Iris variable aperture for SBRT. One week prior to simulation, patients had gold fiducial markers placed via a transperineal or transrectal approach, and were started on a low fiber diet. Patients withheld eating and drinking the morning of and were given a rectal suppository two hours prior to computed tomography (CT) simulation. Contrast-enhanced magnetic resonance images (MRI) were obtained and fused to the treatment planning CT in the treatment planning software using the implanted fiducial markers visualized on MRI heme sequences [19].

CK SBRT planning was performed using the Multiplan 4.5 planning system (Accuray). Target doses and normal tissue tolerances were defined according to the RTOG 0938 protocol guidelines (Supplemental Table I, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.953260). The PTV consisted of the prostate only as defined on non-contrast axial CT and fused T2 MRI with a 3-mm posterior margin and a 5-mm margin in all other directions. Inverse planning was performed using Multiplan 4.5 to generate treatment plans with a prescription dose (PD) of 36.25 Gy in 5 fractions using 6-MV photons. Plans were normalized so that at least 95% of the PTV received the PD or more and the minimum dose to the PTV was 95% of the PD. Dose and dose-volume constraints were applied to the rectum, bladder, penile bulb, femoral heads, and prostatic and membranous urethra as defined on delayed contrast MRI and CT.

Proton planning was performed using the Eclipse planning system (Varian, Inc., Palo Alto, CA, USA). The distal and proximal margins for each treatment field were estimated to be 2.5% of the beam range to the clinical target volume (CTV) plus 1.5 mm. These margins typically ranged from 7 to 8 mm. Ten-mm distal margins were given to the CTVs of the lateral beams and to the distal ranges of the posterior beams to account for rectal filling uncertainties. Field apertures were designed with a uniform 8-mm margin around the PTV to account for the beam penumbra. The smearing margins were set at 5 mm and the smoothing margins at 10 mm. The weightings of the right, left, and posterior beams ranged from 1:1:0.2 to 1:1:0.4. The posterior beam weights were selected based on the plan’s ability to satisfy the dose-volume histogram (DVH) constraints of the femoral heads and bladder. The prescription to the PTV was 36.25 CGE in 5 fractions as determined by the increased relative biological effectiveness of proton radiation,
which is defined to be on average 1.1 as compared to MV range photon radiation. Proton dosimetrists were blinded to the results achieved by the previously generated SBRT plans. Dosimetric indices were compared between the CK and proton plans for each patient and selected parameters were statistically evaluated using the Wilcoxon signed rank test (Table I; see Supplementary Table II for complete indices, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.953260).

Normal tissue complication probability

Normal tissue complication probability for the rectum was calculated using the Lyman Kutcher Berman (LKB) model as previously described [20–24] (see Supplementary Appendix, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.953260). The Lyman parameters TD50, m, and n were obtained for late ≥ grade 2 rectal toxicity from the recent QUANTEC best estimate by Michalski et al. [25]. Rectal DVHs were converted to an equivalent dose based on 1.8-Gy fractions using the linear quadratic (LQ) model and a normal tissue α/β ratio of 3 Gy for late radiation effects. Normal tissue complication probability for the rectum was then calculated using the LKB model as previously described [20–24]. JMP version 10 was used to generate a series of Wilcoxon signed rank sum tests to compare paired protons versus CK SBRT dosimetric data (SAS Institute, Cary, NC, USA).

Results

All 10 patients were treated definitively for localized prostate cancer using CK SBRT so that at least 95% of the PTV received the prescribed dose of 36.25 Gy in 5 fractions. There was significant heterogeneity among patients within the cohort with respect to prostate volume, displaying a range from 14.8 cm³ to 75.0 cm³ and mean prostate volume of 45.1 cm³. Figure 1A shows target and OAR contours for a representative patient along with the resulting CK

| OAR/target          | Dosimetric index | Cyberknife | Proton | p-Value |
|---------------------|------------------|------------|--------|---------|
| PTV                 | V90%             | 99.8%      | 99.99% | 0.002   |
|                     | V100%            | 95.9%      | 95%    | 0.006   |
|                     | V105%            | 78.99%     | 21.57% | 0.002   |
|                     | Mean dose (Gy/CGE) | 39.6      | 37.6   | 0.002   |
| Prostatic urethra   | V100%            | 98.96%     | 99.93% | 0.125   |
|                     | V105%            | 14.85%     | 30.72% | 0.11    |
|                     | Mean dose (Gy/CGE) | 37.6      | 37.9   | 0.014   |
| Rectum              | V25%             | 38.88%     | 21.13% | 0.002   |
|                     | V50%             | 18.83%     | 13.49% | 0.006   |
|                     | V75%             | 8.54%      | 7.99%  | 0.77    |
|                     | V90%             | 3.63%      | 4.37%  | 0.23    |
|                     | V100%            | 0.79%      | 1.09%  | 0.22    |
|                     | V105%            | 0.14%      | 0%     | 0.031   |
|                     | Mean dose (Gy/CGE) | 10.6      | 6.66   | 0.002   |
| Bladder             | V25%             | 73.02%     | 49.32% | 0.004   |
|                     | V50%             | 29.66%     | 37.4%  | 0.037   |
|                     | V75%             | 13.44%     | 25.33% | 0.004   |
|                     | V90%             | 7.14%      | 15.86% | 0.004   |
|                     | V100%            | 3.0%       | 5.82%  | 0.037   |
|                     | V105%            | 0.96%      | 0.02%  | 0.002   |
|                     | Mean dose (Gy/CGE) | 15.4      | 13.7   | 0.56    |
| Penile bulb         | V25%             | 55.33%     | 22.72% | 0.002   |
|                     | V50%             | 20.19%     | 8.61%  | 0.004   |
|                     | V75%             | 3.66%      | 0.69%  | 0.031   |
|                     | Mean dose (Gy/CGE) | 11.4      | 5.19   | 0.002   |
| Membranous urethra  | V75%             | 92.61%     | 86.99% | 0.078   |
|                     | V90%             | 75.93%     | 64.13% | 0.027   |
|                     | V100%            | 45.91%     | 21.0%  | 0.004   |
|                     | V105%            | 9.23%      | 0.13%  | 0.004   |
|                     | Mean dose (Gy/CGE) | 34.4      | 32.2   | 0.006   |
| Right femoral head  | V10%             | 43.5%      | 86.92% | 0.002   |
|                     | V25%             | 3.79%      | 80.69% | 0.002   |
|                     | Mean dose (Gy/CGE) | 7.12      | 10.4   | 0.002   |
| Left femoral head   | V10%             | 82.81%     | 82.31% | 0.77    |
|                     | V25%             | 28.27%     | 76.32% | 0.002   |
|                     | Mean dose (Gy/CGE) | 4.0       | 10.9   | 0.002   |
pencil beam arrangement and plan results. The mean number of CK pencil beams per treatment plan was 147 beams. All CK, and correspondingly generated post-treatment three-field passively scattered proton plans, achieved the defined PTV and organ at risk (OAR) dose constraints as defined by the RTOG 0938 protocol (Supplementary Table I available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.953260).

Patient-averaged DVHs for the PTV, rectum, bladder, penile bulb, membranous urethra, prostatic urethra, and femoral heads were calculated for both CK and post-treatment-generated passively scattered proton plans and are shown in Figures 1B and 2. CK SBRT plans demonstrated a significantly higher mean dose to the PTV as compared to proton planning (39.6 Gy vs. 37.6 CGE; p = 0.002), along with more conformal PD distribution as shown by the conformity index (CI; ratio of total volume receiving 95% of the PD to PTV receiving 95% of the PD), with a mean CI of 1.17 versus 1.72 and p = 0.002 (Figure 1C). However, passively scattered proton plans were more homogenous with an average maximum/minimum PTV dose of 39.15 CGE/30.81 CGE compared to 43.2 Gy/27.6 Gy for the CK SBRT plans.

Patient-averaged DVHs and selected volumetric indices showed a significant reduction in volumes of the penile bulb, rectum, and bladder receiving low doses of radiation as well as the volume of the rectum and bladder receiving more than the PD (Figure 2 and Table I) in the passively scattered proton plans versus the CK SBRT plans. This resulted in a significant reduction in mean dose delivered to the penile bulb (5.2 CGE vs. 11.4 Gy, p = 0.002) and rectum (6.7 CGE vs. 10.6 Gy, p = 0.002). The improvement in the volume of bladder exposed to low doses of radiation in proton planning was offset by the significant reduction in bladder volumes receiving 75% to 100% of the PD in the CK SBRT plans. This difference resulted in a statistically similar mean dose to the bladder in the proton versus the CK SBRT plans (13.7 CGE vs. 15.4 Gy; p = 0.56). In contrast, for the membranous urethra, proton planning showed no improvement over CK SBRT plans in the low dose range, but a significant improvement in volumes receiving 90–105% of the PD (Figure 2 and Table I), resulting in a mean dose reduction of 32.2 CGE versus 34.4 Gy (p = 0.006).

As expected, CK SBRT resulted in a significant improvement over passively scattered proton planning in the mean dose to the left (7.1 Gy vs. 10.4 CGE; p = 0.004) and right (4.0 Gy vs. 10.9 CGE; p = 0.01) femoral heads. There was also a statistically significant difference in mean dose to the prostatic urethra in the CK SBRT plans as compared to the passively scattered proton plans (37.6 Gy vs. 37.9 CGE; p = 0.014); however, this is unlikely to be clinically significant.

To estimate the complication probability of late rectal toxicity with passively scattered proton planning versus CK SBRT planning, individual patient DVHs were converted to 2-Gy equivalent fraction doses and then histogram-reduced as previously described [20–24]. Parameters for the modified Lyman model were obtained from the QUANTEC best overall estimate [25] with a TD50 of 76.9 Gy, n = 0.09, and m = 0.13. This resulted in an estimated NTCP for late ≥ grade 2 rectal toxicity of 13.1% versus 13.9% for CK SBRT versus passively scattered proton plans (p = 0.49).

Discussion
SBRT has become an attractive alternative to conventionally fractionated IMRT for the treatment of localized prostate cancer due to the significantly reduced length of treatment, potential healthcare savings, and early results of prospective trials suggesting equivalent BPFS at five years [9–11]. A recent announcement by the American Society for Radiation Oncology (ASTRO)
Comparing hypofractionated proton therapy and SBRT for prostate cancer suggests that SBRT should now be considered as an appropriate treatment option for low risk and selected cases of intermediate risk prostate cancer [26].

Five-fraction prostate cancer RT treatment requires careful treatment planning with image guidance to accurately deliver the intended PTV dose with sparing of OARs, including the bladder and rectum. RTOG has opened a prospective phase II trial aimed at assessing quality-of-life outcomes as well as acute and late toxicity of two different hypofractionated regimens that can be delivered using highly conformal photon- or proton-based treatment systems. To date, most reported series of prostate SBRT have only included patients treated with photon-based techniques. However, a recent study published by Kim et al. examining different hypofractionated proton therapy treatment schedules for early stage prostate cancer included a 5-fraction arm to a total dose of 35 CGE [27]. At a median follow-up of 42 months, the authors reported late GI and GU ≥ 2 toxicity in the 5-fraction arm of 17% and 11%, respectively. This incidence of ≥ 2 grade 2 late GI toxicity is markedly increased compared to that reported in several photon-based series [9–11,16] employing a higher total dose in 5 fractions with late ≥ grade 2 GI toxicity on the order of 2%. This discrepancy may be explained by the larger PTV margins used in the proton study (7–10 mm) versus the photon studies (3–5 mm), less conservative rectal and bladder dose constraints, differences in image-guided target localization, or differences in interpretation of toxicity severity scoring.

In our study, three-field passively scattered proton plans were generated using identical PTV and OAR contours as the CK SBRT plans, and were subjected to identical DVH constraints. Our results show that dosimetrically acceptable 5-fraction three-field passively scattered proton prostate plans are achievable and also result in significantly improved normal tissue sparing of the rectum, membranous urethra, and penile bulb as demonstrated by the mean dose compared to the CK SBRT plans. Furthermore, the proton plans were consistently more homogenous with a significant reduction in hot spots (volume receiving more than the PD) within the bladder, rectum, membranous urethra, and PTV. In contrast, CK planning resulted in a significantly reduced volume of the bladder receiving high dose radiation (> 90% of the PD) as well as a substantial decrease in mean dose to the femoral heads. These observations are consistent with trends observed in previous dosimetric comparisons of IMRT and proton RT in the treatment of localized prostate cancer [28,29].

In contrast to those studies, we failed to detect any significant improvement using passively scattered proton planning with regards to mean bladder dose, which may result from the three-field geometry used for proton planning in our study, chosen in an effort to create more conformal PTV coverage with reduction in the lateral extent of tissue receiving doses at or in excess of the PD, thus improving the dose delivered to the right and left femoral heads. This method results in anterior/posterior extension of the volume receiving at least 95% of the PD, and is consistent with the rather large difference between the reported average proton conformity index in the Trofimov study compared to the present study: 3.11 versus 1.72 [29]. However, one must consider that the conformity index reported in that study was based on a PTV that included the proximal seminal vesicles, whereas the present study included the prostate only. All two-field generated plans, including anterior or posterior oblique fields, yielded unacceptable doses to the bladder and rectum.

The clinical implications of these dosimetric improvements in normal tissue exposure remain to be seen. We used the LKB model along with parameters obtained from QUANTEC and our extrapolated 2-Gy equivalent fraction data to assess the risk of ≥ grade 2 rectal toxicity between our CK SBRT and passively scattered proton plans. There was no significant difference between the two modalities in this regard; however, the analysis is limited by the lack of modeling data available for radiation fraction sizes in the prostate SBRT range. As prostate SBRT clinical series mature along with long-term quality-of-life data, SBRT-based NTCP models will certainly evolve.

It has been well established that inter- and intra-fraction prostate motion are important factors to
consider during planning of any definitive prostate RT treatment [30–33]. To that effect, intra-fraction prostate proton RT is typically managed using prostate stabilization devices like rectal balloons. These devices limit the degree of antero-postero prostate motion but may also improve the dose delivered to the rectum through manipulation of the rectal volume and spatial relationship to the prostate [34–37]. In the current study, all patients were treated with CK SBRT and therefore underwent simulation without a rectal balloon due to the six-dimensional kV image-based fiducial tracking system that allows for real-time adjustment of the treatment beam for intra-fraction motion. Patients were also placed on a low fiber diet to reduce motility and given a strict bowel preparation regimen before each fraction in an effort to improve inter-fraction variability. Thus, our resulting proton plans may differ slightly from those obtained for patients simulated with a rectal balloon in place. However, it is unclear that placement of a rectal balloon will offer any advantage over the stabilization techniques utilized in our study. Furthermore, any positive change in the spatial relationship between the prostate and rectum will affect both treatment modalities similarly.

Currently, on average, most CK SBRT fractions require a treatment time of 30–40 minutes or more; consequently, all patients were simulated with an empty bladder to maximize patient comfort during treatment. Equivalent ultra-hypofractionated passively scattered proton treatment times are on the order of minutes and would likely be simulated with a full bladder for greater inter-fraction reproducibility and bladder sparing. This is similar to what may be expected with standard linear accelerator-based SBRT using flattening filter-free techniques. Therefore, there may be some change in the bladder dose compared to our study.

Lastly, our study only included the use of passively scattered proton RT because it is the most widely available technology at this time. As intensity-modulated proton therapy (IMPT) becomes more available, it may affect the dose delivered to adjacent normal tissues during prostate RT due to the more conformal dose distribution that is theoretically achievable. IMPT treatment plans have been demonstrated to result in improved normal tissue sparing compared to passively scattered treatment plans in several studies [38,39] and may be expected to further improve the normal tissue radiation exposure defined in this study. However, significant technical limitations remain to be addressed, including target motion and vendor-specific spot-size variability. Also, there is considerable evidence that the often used RBE of proton RT as compared to MV range photon therapy of 1.1 is an oversimplification due to the increased linear energy transfer at the end of the SOBP [40]. Evidence suggests that proton RT RBE actually exists as a continuum that varies based upon distance from the distal edge of the SOBP and α/β ratio of the radiated tissues, with a strong tendency of the RBE to increase as the α/β ratio decreases [40,41]. Long-term prospective studies will be required to demonstrate what effect, if any, this may have on tumor control and late radiation effects.

In conclusion, target and normal tissue dose constraints for ultra-hypofractionated definitive RT of localized prostate cancer are readily achieved using both CK SBRT and passively scattered proton-based RT, suggesting feasibility of either modality. The clinical implications of these results remain to be seen in long-term follow-up of patients receiving ultra-fractionated proton RT for localized prostate cancer.

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Supplementary material available online
Supplementary Appendix, Tables I and II, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.953260