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EFFECT OF ANATOMIC MOTION ON PROTON THERAPY DOSE DISTRIBUTIONS IN PROSTATE CANCER TREATMENT

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Abstract

Purpose—To determine the dosimetric impact of inter-fraction anatomical movements in prostate cancer patients receiving proton therapy.

Methods and Materials—For each of the 10 patients studied, 8 CT scans were selected from sets of daily setup CT images that were acquired from a cohort of prostate cancer patients. The images were acquired in the treatment room using the CT-on-Rails system. First, standard proton therapy and IMRT plans were designed for each patient using standard modality-specific methods. The images, the proton plan, and the IMRT plan were then aligned to the 8 CT images based on skin marks. The doses were recalculated on these 8 CT images using beam from the standard plans. Second, the plans were redesigned and evaluated assuming a smaller CTV-to-PTV margin (3 mm). The images and the corresponding plans were then realigned based on the center of volume of the prostate. Dose distributions were evaluated using isodose displays, dose-volume histograms, and target coverage.

Results—For the skin-marker alignment method, four of the 10 IMRT plans were deficient while three of 10 proton plans were compromised. For the alignment method based on the center of volume of the prostate, only the proton plan for one patient was deficient, while three out of the 10 IMRT plans were suboptimal.

Conclusion—A comparison of passively scattered proton therapy and highly-conformal IMRT plans for prostate cancer revealed that the dosimetric impact of inter-fractional anatomical motions was similar for both modalities.

Keywords

Proton therapy; Image-guided radiotherapy; IMRT; Organ motion

INTRODUCTION

Two recent technological advances have the potential to greatly improve the field of radiation therapy: proton beam therapy and image-guidance. Clinical proton beams, unlike x-ray beams, have a low entrance dose, followed by a region of uniform high dose (the spread-out-Bragg peak) at the tumor/target, then a steep fall-off to zero dose¹. These characteristics make possible a substantial dose reduction to the normal tissues while maximizing the dose to the tumor and give proton therapy an inherent advantage over conformal photon therapy^{2–4}. Simultaneous with increasing interest in proton therapy, there has been a significant advancement in imaging techniques^{5–9}. For example, repeat computed tomography (CT) imaging using in-room CT-on-Rails or cone-beam CT have become available for correcting inter-fractional setup errors or for adaptive replanning^{8, 10–12}.

Repeat imaging is important because the locations, shapes, and sizes of diseased tissue and normal anatomy can change significantly due to daily positioning uncertainties and anatomic changes during the course of radiation treatments as a result of non-rigidity of the body, tumor shrinkage, weight loss, and variations in anatomic contents such as rectal gas and bladder filling in prostate cancer patients^{9–11, 13, 14}. Because of these changes, the three-dimensional (3D) CT images used for radiation treatment planning do not necessarily correspond to the actual position of the anatomy at the time of delivery of each treatment fraction or even to the mean treatment position. The traditional assumption—that the anatomy discerned from 3D CT images acquired for planning purposes is applicable for every fraction—does not take into

account such inter-fractional changes and may ultimately limit the ability to fully exploit the potential of external beam radiotherapy.

For these reasons, there is concern that highly conformal, high-dose intensity-modulated radiation therapy (IMRT) dose distributions designed on the basis of a single CT data set acquired for planning purposes may lead to unforeseen complications or to marginal misses of target volumes due to the inter-fractional movement of the normal structures and the target volumes. It has been argued that proton therapy is more susceptible to tissue density uncertainties than photon therapy¹⁵. Numerous studies have demonstrated changes in the 3D dose photon distribution due to inter-fractional variations in the shapes, sizes, and positions of anatomic structures^{9–11, 13, 14}. To our knowledge, however, there have been no similar investigations for proton therapy. With access to the CT-on-rails system and proton and IMRT treatment planning systems in our institution, we are able to investigate the dosimetric impact of inter-fractional movement of anatomy in patients receiving proton therapy and IMRT.

This goal of this study was to assess the dosimetric effects in prostate cancer patients caused by inter-fractional movement of anatomy in the path of the proton beam. To determine how the 3D dose distributions changed during the course of proton therapy, we undertook a retrospective comparative treatment planning study using repeat CT data obtained from 10 prostate cancer patients that had received IMRT treatments at our institution.

METHODS AND MATERIALS

Patient data

Ten prostate cancer patients previously irradiated by photons at our institution were selected for this study. All patients had a diagnosis of early-stage prostate carcinoma (T2a) and had received IMRT in a linear accelerator suite equipped with the CT-on-Rails system^{10, 11}. Images for each patient were acquired two or three times per week using the CT-on-Rails system just before the treatment. The immobilized patient was positioned on the treatment couch, where the couch was in approximately the treatment position. The couch was then rotated 180 degrees to allow the CT-on-Rails to move into position and acquire an image. The couch was then rotated back to the treatment delivery position. In addition to the initial CT scan acquired for treatment planning, 24 CT scans for each patient were acquired over the course of radiotherapy that included 42 treatment fractions in approximately 8 weeks. For this study, for practical reasons, we selected a subset of 8 CT scans, approximately one scan per week, for each patient. Figure 1 shows the corresponding CT sections for the 8 fractions selected for one of the patients. The prescribed dose for each patient was 75.6 Gy to 98% of the PTV. The CTV included the prostate and the seminal vesicles. The CTV-to-PTV margin for photon IMRT planning was 8 mm, except at the rectum-prostate interface, where it was 5 mm. The repeat CT images were used to study inter-fractional anatomic changes and their dosimetric consequences, not for the modification of actual daily treatment. Contours on all CT scans were drawn manually.

Treatment planning with initial CT images

A commercial treatment planning system (Eclipse; Varian Medical Systems, Inc., Palo Alto, CA) was used for both IMRT and proton therapy plans. The proton beam commissioning data for the treatment planning system were obtained from the Monte Carlo simulations, which showed very good agreement with the measured data. For IMRT planning, each patient plan included eight coplanar, 6-MV beams placed at gantry angles of 25, 60, 100, 150, 220, 260, 300, and 335 degrees (International Electrotechnical Commission scale) were used. The Eclipse inverse treatment planning module generated optimized photon intensity distributions, which were then used to generate leaf sequences, which were in turn used to compute the dose

distribution for the planning CT images. The proton therapy plans were designed using the standard Loma Linda approach with two lateral beams.^{16, 17} The key parameters for proton therapy plans are “border smoothing”, “smearing”, aperture margins, and distal and proximal margins. Most of the planning parameters are selected using the methods described by Moyers *et al.*^{18, 19}. The compensator was designed for the CTV using a custom distal margin that included a 3.5% of depth to account for uncertainty for CT number accuracy and conversion to proton relative linear stopping power and a 3-mm range uncertainty to take into account uncertainties in the accelerator energy, variable scattering system thickness, and compensator density. The distal margin (*DM*) and proximal margin (*PM*) were given by Eq. (1).

$$\begin{aligned} DM &= 0.035 \times \text{CTV distal depth} + 3\text{mm} \\ PM &= 0.035 \times \text{CTV proximal depth} + 3\text{mm} \end{aligned} \quad (1)$$

The aperture margins (*AM*) for all proton beams were drawn to project outside of the CTV by a distance corresponding to the internal target motion margin (*IM*) plus the setup uncertainty margin (*SM*) plus the 90%–50% penumbral width as determined at the widest part(?) of the target, or

$$AM = IM + SM + (90\% - 50\% \text{ penumbra}) \quad (2)$$

The planning system designed the range compensators using a simple ray-tracing from the virtual proton source position (about 270 cm from iso-center) through the CTV. If the compensator thickness outside of the region included in the ray tracing procedure were set to the maximum thickness, protons would scrape along the walls of the ray-traced region of the compensator wherever the compensator is not shielded by the block. To avoid this effect, a “border-smoothing” margin (*BSM*) was specified in the planning system to set the compensator thickness *t* not shielded by the block to the average thickness of the compensator traced by the ray and located within a circle centered at *t* with a radius defined by the *BSM*. The *BSM* is not a critical parameter, and the default value (1 cm) was used.

In proton therapy, uncertainty in aligning the compensator to the patient and possible motion of the patient during treatment can create cold spots in the target. To guarantee target coverage, the compensator was “smeared” using the algorithm from Urie. *et al.*²⁰ and implemented in the TPS. It compares each pixel of the ray tracing compensator with the pixels inside the smearing margin and sets the pixel value to the minimum of the neighboring pixels. In our proton therapy plan design, the smearing parameter was selected on the basis of the formula by Moyers *et al.*¹⁸, or

$$\text{Smearing} = \sqrt{(IM + SM)^2 + [0.03 \times (\text{distal CTV depth} + \text{compensator thickness})]^2}, \quad (3)$$

where *IM* is the internal margin and *SM* is the setup margin. For prostate plans, we set the *IM*=0. The *SM* was set to values derived from the CTV-to-PTV expansion. For all the fields in this study, the distal CTV depth was about 24.4±0.8 cm, and the proximal CTV depth was about 15.2±1.5 cm. A typical compensator thickness for prostate treatments with our system is 5.8±1.1 cm of Lucite. Combining these values and evaluating Eq. (3), we obtained a smearing parameter value (radius) of approximately 1.2 cm for a typical prostate case. It is noteworthy that Eq. (3) actually implies that smearing plays two roles. First, it compensates for intra-fractional and inter-fractional variations in tissue densities in the path of the beam. Second, it mitigates against the consequences of the approximations in the design of compensators. In the current state of the art, the water-equivalent compensator thickness along each ray is set to the water-equivalent thickness through the tissues to the distal edge of the target plus the margin. The lateral transport of radiation is ignored. However, when the dose distribution is

calculated using such a compensator, defects in the form of hot and cold spots may appear near the end of the range. Smearing serves to minimize such defects.

Analysis of repeated CT images

The proton therapy and IMRT plans designed using the planning CT images were aligned with each of the selected subset of eight repeat CT images based on the skin marks and on the center of volume of the prostate. The dose distributions were then recalculated for the repeat CT images using the same beam portals (i.e., the same beam range, SOBP width, aperture, range compensators, normalization, etc. for the proton therapy plans and the same energy, multi-leaf collimator leaf-motion patterns for the IMRT plans). For plans computed using the skin-marker alignment, a CTV-to-PTV margin of 5 or 8 mm, currently used at M. D. Anderson for IMRT, was used for plan evaluation. For the plans using the prostate center of volume (PCOV) alignment method, a uniform 3-mm CTV-to-PTV margin was used. We term the plans recalculated using the repeat CT images as repeat CT plans.

Because contours on repeat CT images had already been delineated, for this study, we used the average volumes receiving the indicated doses or higher for the rectum, bladder, and CTV over the eight fractions to approximate the dose and volume data for the plan delivered during the course of the treatment. We termed the average volume receiving the indicated dose as the “recalculated volume receiving the delivered dose” in the remaining discussion. It should be noted that using the average volumes receiving specified doses over multiple fractions may not be a valid concept. Individual voxels change position and, in some situations, volumes contained within voxels may also change. Ideally, deformable registration should be used to track individual voxels and compute a biologically equivalent dose for each voxel. The data shown here, however, are sufficient to give a qualitative sense of the fraction-to-fraction variability of dose-volume combinations.

RESULTS

Comparison of IMRT and proton therapy plans

Typical dose distributions in transverse and sagittal planes for the original IMRT and proton therapy plans are shown in Fig. 2. All dose distributions were normalized to 98% of the prescribed dose to the PTV (75.6 Gy). Figure 3 compares the corresponding dose-volume histograms (DVHs) for the CTV, PTV, bladder, femoral heads, and the rectum. The IMRT plan had slightly lower dose homogeneity in the PTV and CTV as a consequence of conformal avoidance of nearby critical structures, i.e., the rectum and bladder. The proton therapy plan was better at sparing the rectum at doses of less than 50 Gy. However, above 50 Gy, IMRT was better at sparing the rectum. The body mean nontarget (excluding PTV) integral dose was 6 Gy for the IMRT plan and 3.6 Gy for the proton therapy plan, indicating that the non-target integral dose was 1.7 times higher for the IMRT plan than for the proton therapy plan. The proton therapy plan spared the bladder better than IMRT plans for doses below 45 Gy, but at higher doses the two plans were very similar. We also calculated the conformality index (PTV volume/prescribed dose volume) for the patient shown in figure 2. The conformality index for the IMRT plan is 1.16 and proton plan is 1.33. The main reason for large lateral treatment volume was that we selected the distal margin (L-R direction) based on the 3.5% CT number uncertainties, which is about 1.2 cm larger than the 0.3 cm margin chosen for the photon IMRT plan in L-R direction. Figure 3 illustrates the differences between an IMRT and a proton plan. This case is representative of the 10 cases studied in this work. On the basis of dose considerations, these results suggest that the proton plan provides a significantly lower integral dose to healthy tissues and comparable target coverage and avoidance of critical structures.

An analysis of the irradiated tissue volumes generally confirmed the results of dose analysis described above. In Tables 1 and 2, we present average volumes of the rectum and bladder receiving at least the indicated doses with the proton therapy plans (column III) and IMRT plans (column V) using a uniform 3-mm CTV-to-PTV margin (Table 1) and a larger margin (8-mm CTV-to-PTV margin except 5-mm margin at rectum and prostate interface) (Table 2). The volumes were averaged over 10 patients. Similarly to the case shown in Figs. 2 and 3, at doses less than 50 Gy, the proton therapy plan was superior in sparing the rectum. For doses higher than 50 Gy, IMRT plans spared the rectum better. We also calculated the differences in normalized volume for the rectum between the plans using larger and smaller margins at various doses. The data show a potential dosimetric benefit with smaller margins when using the CT-guided techniques for patient setup. Reducing the margin size resulted in more rectal sparing improvements in the proton therapy plans than those on the IMRT plans. The volumes receiving doses of 30, 40, 50, 60, and 70 Gy were reduced by 8.7%, 9.3%, 9.2%, 8.9%, and 7.7%, respectively, for the proton therapy plans when the CTV-to-PTV margin was reduced to 3 mm; the corresponding values for the IMRT plan were 5.4%, 4.7%, 5.1%, 5.7%, and 6.0%.

For the bladder, at doses less than 50 Gy, the proton therapy plan produced superior results. At doses higher than 50 Gy, IMRT plans and proton therapy plans had similar sparing of the bladder. Reducing the CTV-to-PTV margin from 8 mm to 3 mm resulted in a larger reduction in dose to the bladder in proton therapy plan than in the IMRT plan. Specifically, the volumes receiving doses of 30, 40, 50, 60, and 70 Gy were reduced by 5.1%, 4.9%, 4.7%, 4.5%, and 4.0% for the proton therapy plans; the corresponding values were 5.1%, 4.6%, 4.1%, 3.7%, and 3.3% for the IMRT plan. On average, reducing the margin had less effect on bladder sparing than on rectal sparing for both proton and IMRT plans.

Table 1 also presented the recalculated volume receiving various dose or higher for the rectum, bladder, and clinical target volume for both IMRT and proton repeat CT plans. The Table compares dose and volume data (averaged over ten patients) from the pretreatment proton and IMRT plans. The recalculated volume data were averaged over the eight fractions using a uniform 3-mm CTV-to-PTV margin and the CT-guided alignment method. Similar to the original plan, at doses less than 50 Gy, the proton therapy plan produced superior results. For doses above 50 Gy, the IMRT plans spared the rectum better. From the results in Table 1, we calculated the differences between the original plans and repeat-CT plans in the normalized volume of the rectum that received doses of 30, 40, 50, 60, and 70 Gy. The volumes increased by 4.6%, 5.6%, 6.3%, 7.1%, and 7.8%, respectively, from the original plans to the repeat-CT plans for proton therapy; the respective values were 2.9%, 8.6%, 7.4%, 7.3%, and 7.9% for the IMRT plans. At most doses, the differences between the normalized volumes for the repeat CT plans and those for the original plans were smaller for proton therapy than for IMRT.

Repeat-CT proton therapy plans spared the bladder better than the repeat-CT IMRT plans for all dose levels. We also calculated the differences between normalized volume for the original plans and the repeat CT plans in the normalized volume of the bladder that received doses of 30, 40, 50, 60, and 70 Gy. The volumes increased by 10.8%, 9.1%, 7.5%, 6.0%, and 4.1%, respectively, for the proton therapy plans from the original plans to repeat CT plans; the respective values were 20.7%, 15.7%, 11.7%, 8.0%, and 5.1% for the IMRT plans. At all doses, the differences between the volumes of the repeat CT plans and volumes for the original plans were smaller for the proton plan than for the IMRT plan.

For the plans using a larger margin (8 mm CTV-to-PTV margin except 5mm at rectum and prostate interface), we used the skin-mark alignment method to calculate the actual dose-volume data. Table 2 presents volumes receiving various doses or higher for the rectum, bladder, and clinical target volume for both IMRT and proton repeat CT plans. The values were averaged over the ten patient cohorts. A comparison of these values to the corresponding dose

volume data for the pretreatment proton and IMRT plans revealed that the differences between the original-CT based plans and the repeat-CT plans were similar to the corresponding differences in dose volume data using the CT-guided alignment method and a smaller CTV-to-PTV margin.

Target dose distribution for proton and IMRT repeat CT plans

Figure 4 plots the average differences between the center of volume of the prostate and the skin marker position over eight fractions for the 10 patients in the right-left (Fig. 4a), anterior-posterior (Fig. 4b), and superior-inferior (Fig. 4c) directions. The error bars indicate the standard deviation. Figure 4d shows the magnitude of the differences in the three directions. The difference between the center of volume of the prostate and the skin marker position was largest in the anterior-posterior direction. This difference exceeded 0.5 cm for three patients (patients 2, 4, and 9). In the superior-inferior direction, the difference exceeded 0.5 cm only for patient 9. In the right-left direction, the difference for all patients was less than 0.5 cm. Figure 4d shows that the magnitude of the difference was the largest for patient 9. Figure 5a shows the normalized CTV volume receiving the prescribed dose (75.6 Gy) averaged over the eight fractions using the skin-marker alignment method for both the IMRT and proton plans. If 97% of the CTV or more receives the prescribed dose, the plan is considered acceptable, otherwise it is considered to unacceptable due to compromised target coverage. Using the skin-marker alignment technique, the proton therapy plans for 3 of 10 patients (patients 2, 4, and 9) were unacceptable. These patients exhibited larger differences between the center of volume of the prostate and skin marker position in the anterior-posterior direction than other patients did. When the difference between the center of volume of the prostate and the skin marker position exceeded 5 mm, which is the smallest CTV-to-PTV margin, both the proton and IMRT plans would have compromised target dose coverage. For the skin-marker alignment method, 4 (patients 2, 3, 4, and 9) out of the 10 IMRT plans were unacceptable. The proton therapy plans are more tolerant of daily setup variations. The average CTV volume receiving the prescribed dose was 96.3% for the proton therapy plans and 94.1% for the IMRT plans.

Figure 5b shows the normalized CTV volume receiving the prescribed dose (75.6 Gy) averaged over the eight fractions with repeat CT scans aligned using the center of volume of the prostate. The original plans were designed using a uniform 3-mm CTV-to-PTV margin. For the proton therapy plans, only the plan for patient 9 is unacceptable, where as three (patients 1, 3, and 9) out of the 10 IMRT plans are unacceptable. Here also the proton therapy plans are more tolerant of daily setup variations. The average volume receiving the prescribed dose for CTV was 98.2% for the proton plans and 95.6% for the IMRT plans.

DISCUSSION

There are numerous differences between proton- and photon-beam therapy that have significant consequences with respect to planning and delivery of treatments. Common to both modalities, however, is an incomplete understanding of the uncertainties in the dose distributions that are actually delivered to prostate therapy patients, especially those uncertainties introduced by inter-fraction anatomical motions. Protons have a finite range and a monoenergetic proton beam is expected to virtually stop at a well-defined depth when incident normally on a flat homogeneous medium. Uncertainties related to CT numbers, stopping powers, motion, positioning, etc. affect protons and photons quite differently. As a consequence, the depth at which the protons really stop is uncertain. Furthermore, the presence of inhomogeneities and compensators may degrade the proton range significantly. At the same time, component of translational motion for the body as a whole has virtually no effect on proton dose distributions; however, variation in water-equivalent path length to the proximal and distal edges of the CTV must be accounted for. In addition, as compared to photons, protons scatter significantly

differently from inhomogeneities and other objects in their path and may create hot and cold spots in regions distal to inhomogeneities. Moreover, commonly used algorithms can only approximately account for proton scattering. Thus, what is seen on a treatment plan is an approximation of what is actually delivered. Decades of experience with proton therapy have resulted in empirical strategies to minimize the impact of these uncertainties. One such strategy is the way in which margins are chosen. For photons in which a PTV is defined to account for positioning and motion uncertainties and margins of all beams are set to produce target dose distributions that adequately cover the PTV. In contrast, for protons, margins must be defined for each beam. The proximal and distal margins are set so as cover the CTV in the presence of uncertainties in the range of protons caused by factors mentioned above (see Eq. 1). Surprisingly, our results suggest that when the difference between the center of volume of the prostate and the skin marker position exceeded 0.5 cm, which is the smallest CTV-to-PTV margin, both the proton and IMRT plans would have caused the target to be compromised. This implies that major reason for compromising the target coverage for the proton plan in this work is set-up errors, rather than proton range errors, would be the predominant cause of inadequate target coverage in prostate patients planned.

Moyer et. al.¹⁸ argued that use of the PTV concept should be abandoned for the charged particle beams based on the treatment plan design for the lung patients. However, based on this work, we would argue that PTV concept could be used in the special case of a lateral opposed-pair field arrangement for treatment of the prostate. To illustrate this point, we designed a study to show the effect of the set-up uncertainty and range uncertainty on the prescription dose line. Figure 6 shows the original prescription line, and the prescription lines when the patient was moved 5 mm each in anterior, posterior, superior, inferior, right, and left direction and stopping power for the tissue increased/decreased 3.5% for a parallel two-beam proton plan from right and left directions. In the directions perpendicular to the beam direction, if the patient moves 5mm, the prescription iso-dose line will shift 5 mm accordingly. This is very similar to the iso-dose line change for a photon plan.

However, for the proton plan, we must also consider the range uncertainty along the beam direction. If the patient moves 5 mm along the beam directions, the corresponding prescription dose lines were identical to the original dose line. This behavior is unique to the parallel opposed-pair proton beam arrangement. From figure 6, it indicates that target is well covered even if the range was increased or decreased 3.5%. Although the PTV for the proton plan is not exactly the same as that for the photon plan, if the prescription requires 98% of PTV receiving prescription dose for the photon plan, it is also convenient to require 98% photon PTV receiving prescription dose for the proton plan in order to ensure the target coverage for the direction perpendicular to the beam directions. In a recent study, Thomas et. al.²¹ showed that the PTV margin can be reduced in the axial direction but no reduction can be seen in other directions for prostate proton plans compared with photon plans. Although Thomas et. al.'s study did not consider the range uncertainties, the estimation of the set-up uncertainties in the direction perpendicular to the beam directions agree with our results.

In the design of the proton plan, it is essential to use smearing to compensate for intra-fractional and inter-fractional variations in tissue densities in the path of the beam. With the use of these margins and with the use of smearing, we found that the proton therapy plans are no more sensitive to inter-fractional variations in anatomy than the highly-conformal IMRT plans.

We observed that the CTV was not adequately covered for some patients (e.g., patient 9) even when the prostate center of volume method was used. The main reason is that the CTV for this patient included both the prostate and the seminal vesicles. The CT-guided method proposed in this study uses only the prostate as the reference for setting up treatments. The seminal vesicle sometimes did not move with the bulk of the prostate. Table 3 shows the CTV, prostate,

and seminal vesicle volumes receiving the prescribed dose (75.6 Gy) for the 8 daily CT plans for both the proton therapy and IMRT plans for patient 9. The prostate was adequately covered by both the IMRT and proton therapy plans, but the seminal vesicles were under-dosed.). For this patient, the 97% of the seminal vessel received at least 60 Gy for both IMRT and proton plans. However, even in this worst case, the proton therapy plan was less sensitive to inter-fractional variation than the IMRT plan was.

Although comparing treatment planning for IMRT and proton therapy was not a main focus of this study, we observed that the IMRT plans were better at sparing the rectum at doses higher than 50 Gy for most patients. We observed that if we only treated partial seminal vessels (proximal seminal vessels), proton plan would normally yield better rectum sparing at doses higher than 50 Gy. Another reason for this is that only two lateral beams were used for the proton treatment plans. To study this further, we designed another proton plan for one of the patients using four beams—two lateral, parallel opposed beams and two oblique beams. Figure 7 shows the dose distributions in transverse planes for an IMRT plan (a), the proton beam with four beams (b), the proton plan with two parallel-opposed beams (c), and the dose-volume histograms (d) for the PTV, rectum, and bladder. Rectum sparing for doses higher than 50 Gy is very similar for IMRT and the four-beam proton plans. For doses less than 50 Gy, the four-beam proton plan is better at rectum sparing than the IMRT plan. We also observed that the better sparing of the rectum by the four-beam proton plan was achieved at the expense of bladder sparing.

The main reason why most proton centers do not use such four-beam or similar multi-beam approaches is that the oblique beams would be aimed at the rectum. For proton therapy, there is a substantial uncertainty in where the beam actually stops. In addition, there is uncertainty in biological equivalence of the physical proton dose compared to the same photon dose. The radiobiological effectiveness (RBE) of proton dose known to increase with depth and is higher for lower doses. Such variations in RBE are ignored and a fixed value of 1.1 is currently used. To avoid the consequences of range uncertainty and RBE approximations, a rule of thumb in proton treatment planning is adopted, which is not to aim the proton beam toward the critical organs in the proximity. We believe that the quality of proton therapy planning will improve significantly if uncertainties in range and RBE are reduced.

CONCLUSION

Inter-fractional variations in volumes, positions, and shapes of targets and critical normal tissues can be significant. However, for proton therapy plans designed using the passive scattering technique, changes in the dose distribution due to inter-fractional anatomic changes were no worse than those for IMRT plans when adequate consideration was given to the additional uncertainties caused by proton beams.

We believe that there is considerable potential for better control of the range uncertainties for proton beams and further improvement of proton treatment planning techniques, which will be needed for intensity- and energy-modulated proton therapy.

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Fig 1.
CT images acquired on eight treatment fractions for a prostate cancer patient (transverse and coronal views). The images were aligned as if the patient were set up using skin landmarks. The red color wash shows the prostate, the red contour shows the rectum, and cyan shows the bladder.

Fig 2.
The dose distributions in a transverse plane (top panel) and in a sagittal plane (bottom panel) for an IMRT plan (left panel) and a proton therapy plan (right panel).

Fig 3.

Dose-volume histograms for the PTV, CTV, rectum, femoral heads, and bladder for a prostate cancer case. The solid and dashed lines show the results calculated using IMRT and proton beams, respectively.

Fig 4.

The mean differences between the center of volume of the prostate and skin marker position over the eight fractions for the 10 patients in (a) the right-left direction, (b) the anterior-posterior direction, and (c) the superior-inferior direction. The error bars indicate the standard deviation; (d) shows the magnitude of the differences in the three directions

Fig 5. Recalculated normalized CTV receiving the prescribed dose (75.6 Gy) over the eight fractions for the 10 patients using (a) the skin-marker alignment method and (b) the method using the center of volume of the prostate for both the IMRT and proton repeat-CT plans.

Fig 6.

The prescription dose line, and the prescription dose lines when the patient was moved 5mm each in anterior (green), posterior (cyan), superior (pink), inferior (orange), right (blue), and left (brown) direction and stopping power for the tissue increased (black)/decreased(white) 3.5% for a parallel two-beam proton plan from right and left directions. The color washed blue shows the CTV and color washed green shows the CTV expanded uniformly 5mm.

Fig 7.

Dose distributions in transverse planes for an IMRT plan (a), a proton beam with four beams (b) and a proton plan with two parallel opposed beams (c) and the comparison of dose-volume histograms (d) for the PTV, rectum, and bladder in the prostate cancer case. The solid and dashed lines show the results calculated using four oblique proton beams and two parallel opposed lateral beams, respectively. The dotted line shows the results using IMRT.

Table 1 Prostate dose-volume data averaged over eight fractions and over ten patients. The data are for the original plan, and for the original plan applied to subsequent fractions with set-up based on prostate center of volume. The original plans were designed using a uniform 3mm CTV to PTV expansion margin.

ROI	Dose (Gy)	Pre-RT (proton)	CT-guided registration (proton)	Pre-RT (IMRT)	CT-guided registration (IMRT)
Rectum	30	47.8	52.4	61.7	64.5
	40	39.7	45.3	46.8	55.4
	50	32.1	38.3	33.4	40.8
	60	23.7	30.8	21.5	28.8
Bladder	70	13.8	21.6	9.5	17.4
	30	12.9	23.7	21.8	42.5
	40	10.9	20.1	15.8	31.6
	50	9.0	16.6	11.6	23.2
CTV	60	7.1	13.1	8.0	16.0
	70	4.8	8.9	5.2	10.3
	75.6	100.0	98.2	100.0	95.6

Prostate dose-volume data averaged over eight fractions for the ten patients. The data are for the original plan, and for the original plan applied to subsequent fractions with set-up based on skin-marker. The original plans were designed using a larger CTV-to-PTV margin, currently used at M. D. Anderson for IMRT

Table 2

ROI	Dose (Gy)	Pre-RT (proton)	Skin mark registration (proton)	Pre-RT (IMRT)	Skin Mark registration (IMRT)
Rectum	30	56.5	54.1	67.1	71.0
	40	49.0	47.5	51.5	55.2
	50	41.2	40.8	38.5	40.9
	60	32.6	33.4	27.2	29.4
Bladder	70	21.6	24.2	15.5	19.4
	30	18.1	31.8	26.9	48.7
	40	15.9	28.3	20.4	38.5
	50	13.8	25.0	15.7	30.6
CTV	60	11.6	21.3	11.7	23.2
	70	8.8	16.6	8.5	17.4
	75.6	100.0	98.2	96.2	94.5

The CTV, prostate, and seminal vesicle volumes receiving the prescribed dose (75.6 Gy) for the 8 daily CT plans for both proton and IMRT plans for patient 9.

Daily CT #	IMRT		Proton	
	CTV	SV	Prostate	SV
1	86.5	53.7	97.2	76.5
2	88.1	56.5	98.8	78.6
3	87.6	57.7	98.0	84.3
4	88.0	55.1	97.5	70.7
5	83.0	44.7	98.3	73.1
6	85.9	53.1	97.2	77.5
7	86.4	62.0	96.9	83.4
8	86.1	52.7	97.6	72.7