Published in final edited form as:

Med Dosim. 2020 ; 45(3): 264–270. doi:10.1016/j.meddos.2020.01.005.

Dosimetric evaluation of MR-derived synthetic-CTs for MR-only proton treatment planning

David Aramburu Núñez, Ph. D.^{*}, Sandra Fontenla, MS^{*}, Lauren Rydquist, BS[‡], Gabriely Del Rosario, BS[‡], Zhiqiang Han, BS[‡], Chin-Cheng Chen, Ph. D.[‡], Dennis Mah, Ph.D.[‡], Neelam Tyagi, Ph. D.^{*}

^{*}Memorial Sloan Kettering Cancer Center; 1275 York Avenue, New York City, NY 10065

[‡]ProCure Proton Therapy Center; 103 Cedar Grove Lane, Somerset, NJ 08873

Abstract

Purpose—To evaluate proton dose calculation accuracy of optimized pencil beam scanning (PBS) plans on MR-derived synthetic-CTs for prostate patients.

Methods—Ten patient datasets with both a CT and an MRI were planned with opposed lateral proton beams optimized to single field uniform dose under an IRB-approved study. The proton plans were created on CT datasets generated by a commercial synthetic CT-based software called MRCAT (MR for Calculating Attenuation) routinely used in our clinic for photon-based MR-only planning. A standard prescription of 79.2 Gy (RBE) and 68.4 Gy (RBE) was used for intact prostate and prostate bed cases, respectively. Proton plans were first generated and optimized using the MRCAT synthetic-CT (syn-CT), and then re-calculated on the planning CT rigidly aligned with the syn-CT (aligned-CT) and a deformed planning CT (deformed-CT), which was deformed to match outer contour between syn-CT and aligned-CT. The same beam arrangement, total MUs, MUs/spot, spot positions were used to recalculate dose on deformed-CT and aligned-CT without re-normalization. DVH analysis was performed on aligned-CT, deformed-CT and syn-CT to compare D_{98%}, V_{100%}, V_{95%} for PTV, PTV_{eval} and GTV as well as V_{70Gy}, V_{50Gy} for OARs.

Results—The relative percentage dose difference between syn-CT and deformed-CT, were (0.17 ± 0.33 %) for PTV_{eval} D_{98%} and (0.07 ± 0.1 %) for CTV D_{98%}. Rectum V_{70Gy}, V_{50Gy}, and Bladder V_{70Gy} were (2.76 ± 4.01 %), (11.6 ± 11.2 %), and (3.41 ± 2.86 %), respectively for the syn-CT, and (3.23 ± 3.63 %), (11.3 ± 8.18 %), and (3.29 ± 2.76 %), respectively for the deformed-CT, and (1.37 ± 1.84 %), (8.48 ± 6.67 %) and (4.91 ± 3.65 %), respectively for aligned-CT.

Conclusion—Dosimetric analysis shows that MR-only proton planning is feasible using syn-CT based on current clinical margins that account for a range uncertainty.

Corresponding author: David Aramburu Núñez, Ph. D., aramburd@mskcc.org, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York City, NY 10065.

Conflict of Interest Statement

Memorial Sloan Kettering Cancer Center has a master research agreement with Philips Healthcare.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

MR-only; Proton Therapy Planning; Synthetic CT; Prostate

1. Introduction

Accurate tumor delineation is crucial to deliver high doses to the target while sparing organs-at-risk (OARs) with sharp dose gradients. MRI has been utilized in radiation oncology over the past decade and has shown a reduction in systematic errors in contouring numerous disease sites¹. In prostate cancer patients, the American College of Radiology suggests the use of MRI to delineate a sensitive tumor incidence area, the apex of the prostate, which cannot be seen in Computed Tomography (CT) alone². Tumor burden in brain patients can also be more clearly resolved in MRI than in CT^{2,3}.

However, CT is still the primary imaging modality used for photon and proton planning dose calculations. Current workflows, including MRI, relies on CT-MRI registration, transferring contours from one image set to other, leading to geometrical uncertainties^{4,5}. An MR only workflow is therefore desirable as it can remove systematic CT-MRI registration uncertainties as well as improve patient workflow efficiency and reduce radiation dose to the patient and imaging costs. Accurate mapping of electron densities from MR images has been a challenge due to the lack of one-to-one correspondence between the two. Recent studies have shown the feasibility of MR-based radiotherapy planning (MR-only) using synthetic-CTs (syn-CT) generated from MR^{6,7}. In addition, commercially available solutions for synthetic CT generation have also been tested and implemented for certain sites like prostate and brain^{8,7}. The clinical feasibility of MRI-only in photon planning has been proven using the MR simulator as well as the new state of the art MRI-Linacs^{9,10}.

Proton therapy for prostate cancer patients has improved the radiation therapy treatment due to a reduction in integral dose to the patient as compared to Intensity modulated radiation therapy (IMRT)¹¹. MR-only planning for protons is very appealing as it minimizes dosimetric errors introduced by misregistration between the planning CT and MR or changes in anatomy between the two scans. Once implemented in the clinic, it can improve efficiency, reduce redundant imaging and minimize patient inconvenience. Proton MR-only planning has the potential to provide high accuracy organ delineation, reduce normal tissue toxicity and deliver higher doses to the target. Previous works using MR derived syn-CT generation approach have shown the feasibility of MR-only proton planning^{12,13}. The main challenges encountered were related to the assignment of stopping power ratios relative to water in air and bone regions, which led to some significant dosimetric differences.

Maspero et al were the first to use a commercially available solution to show the feasibility of MR-only proton dose calculation compared with CT¹⁴.

In our study, we have adapted a well-established prostate photon planning MR-only clinical workflow to proton planning⁷.

2. Material and Methods

2.1. Patient data collection and simulation

Ten prostate patients were enrolled in this study (Table1). Patients were diagnosed with prostate adenocarcinoma, intermediate to high risk with Gleason Score ranging from 7 to 9. Out of ten patients, nine had intact prostate glands and one was post-operative prostate bed. Patients included were between 52–85 years old with a median age of 75.5 years. Each patient underwent a photon-based MR-only workflow as previous described by Tyagi et al on a 3T Ingenia Philips scanner⁷. MR simulation was performed with patients on an indexed flat table with custom immobilization. A backup CT simulation was performed in exactly the same MR conditions, in order to minimize positional discrepancies. For both MR and CT studies, patient simulation included the following: foley catheter, knee roll, indexed flat tabletop, and a thermoplastic anterior Aquaplast immobilization mold. In 9 patients with intact prostate, three gold fiducial markers of 3mm length and 1.2 mm diameter were implanted into the prostate using ultrasound guidance, with the goal of monitoring the prostate position before and during radiation treatment. It's also our institutional practice to insert hydrogel rectal spacer into patients undergoing high dose SBRT. Five patients had spacer while five patients were scanned without spacer.

2.2. CT and MRI acquisition

The MR simulation protocol consisted of a small FOV 2-D axial turbo spin echo T2-weighted (T2w) sequence (TR/TE = 5200/100 ms, bandwidth = 257, slice thickness= 3 mm, FOV = 230×222×199 cm³, voxel size = 0.65×0.83×4 mm³, NSA = 3) for soft tissue delineation, a 3-D dual-echo fast field echo (FFE) mDIXON MRCAT (TR/TE1/TE2 = 3.8/1.21/2.4, BW = 1072 Hz, slice thickness = 2.5 mm, FOV = 368×552×300 cm³, voxel size = 1.7×1.7×2.5 mm³) sequence for synthetic CT (syn-CT) generation, 3-D balanced FFE-based sequence TR/TE = shortest (3.8/1.9), T2/T1, FOV = 180×180×90 cm³, voxel size = 0.6×0.6×1.00 mm³, NSA = 2) for fiducial identification. A CT acquisition (Aligned-CT) was acquired on a 16 slice CT scanner with 2.5 mm slice thickness. All aligned-CT images were deformed to match the MR mDIXON source image generating deformed-CTs.

Synthetic CTs (syn-CT) were generated at the MR console using a commercial synthetic CT software called MRCAT. The software uses a single mdixon MR sequence along with a constrained shape model to estimate body contour and to segment bone structures. Five tissue types (Air, muscle, fat, cortical bone, soft bone) are classified, and a bulk electron density is assigned to these tissues to generate a synthetic CT. Values assigned to each type tissue are in agreement with hounsfield units values obtained from regular CTs as shown in Figure 1.

During MR simulation, three MR compatible BB's are placed at the reference points to make them visible in the treatment planning system for defining the isocenter on the syn-CT by triangulating on these BB's.

2.3. Treatment planning

Two assessments were made to evaluate the accuracy of the syn-CT for proton treatment planning. First, the treatment plan and structure set from the syn-CT were transferred to the aligned-CT for all ten patients and dose was recalculated on aligned-CT without renormalization and then compared. Second, to avoid inter-scan variabilities between the aligned-CT and syn-CT images, a deformed-CT was created. The aligned-CT was deformed to the MR mDIXON source sequence to create a deformed-CT image. Rigid registration between syn-CT and deformed-CT was easily performed, due to syn-CT is an image set derived from MR mDIXON. This multi-step process was used previously by Tyagi et al ⁸.

Radiation treatment plans on the syn-CTs for ten prostate patients were performed on the treatment planning system RayStation (v6.1.1.2 Raysearch Laboratories, Stockholm, Sweden) using two opposed lateral pencil beam scanning (PBS) fields with single-field optimization. A standard prescription of 79.2 Gy (RBE) in 44 fractions, and 68.4 Gy (RBE) in 38 fractions, was used for intact prostate and prostate bed cases, respectively. The same beam arrangement, total MUs, MUs/spot, spot positions were used to recalculate dose on deformed-CT and aligned-CT without re-normalization.

For all ten patients, CTV and OARs such as rectum and bladder were contoured by an experienced radiation oncologist on the axial T2. The CTV consisting of prostate only was expanded differently for non-spacer and spacer patients. The margins from the CTV in non-spacer patients were 0.2 cm posterior and 0.3 cm elsewhere to generate the PTV. For spacer patients, a margin of 0.3 cm was given to the CTV in all directions to generate the PTV. PTV_{eval} for both scenarios was generated using a lateral margin of 0.5 cm to the PTV to take into account proton range uncertainties. Distributions are planned to cover PTV_{eval} which is sufficient to also deal with changes in radiological path length due to organ motion¹⁵. Targets and OARs for all patients were rigidly transferred from syn-CT to aligned-CT and deformed-CT after registration. OARs were adapted and recontoured, as needed, on the aligned-CT and deformed-CT, respectively. To assess the absolute average dose difference between aligned-CT and deformed-CT with respect to syn-CT a new structure with an internal margin of 1 cm from the external contour was created (inner body). This was done to eliminate the effect of three external MR compatible BB's that were used to define the isocenters. In the current study, the BBs were not eliminated from the scan during proton planning, as done clinically. As a result, the BBs absorbed dose when the lateral beams passed through them. The BBs were not present during the CT simulation nor during treatment.

2.4. Dosimetric Evaluation

Treatment plan and target structure set were transferred from syn-CT to aligned-CT and deformed-CT, respectively. Structure sets for OAR were adjusted on each image set due to possible differences in patient setup between image modalities. Finally, dose was recalculated on aligned-CT and deformed-CT without re-normalization.

DVH analysis was performed to compare D_{98%}, V_{100%}, V_{95%} for PTV, PTV_{eval} and CTV on aligned-CT, deformed-CT and syn-CT, respectively. Rectum V_{50Gy}, V_{65Gy}, V_{70Gy}, and

Bladder $V_{70\text{Gy}}$ were also compared on all three image data sets. Relative percentage differences between aligned-CT and deformed-CT with respect to syn-CT were calculated for all DVH parameters. The dosimetric parameters were also compared between spacer and non-spacer group.

The absolute dose difference between aligned-CT and deformed-CT with respect to syn-CT were assessed using dose module in MIM™ software

A 2D gamma analysis through the isocenter plane was performed between syn-CT and aligned-CT as well as syn-CT and deformed-CT, respectively. A gamma pass rate criterion of 3%/3mm with a dose cut off of 50% and 2%/2mm with a dose cutoff of 10% was chosen for evaluation.

3. Results

Dose evaluations of clinically relevant DVH parameters between aligned-CT and deformed-CT with respect to syn-CT were calculated and illustrated in Figures 2 and Figure 3 for target volumes and, Figures 4 and Figure 5 for OARs.

The absolute average dose difference (mean $\pm$ SD) between aligned-CT and deformed-CT with respect to syn-CT was calculated in the inner body volume to assess the variability of inter-scan factors. The dose difference for deformed-CT was (5.64 ± 2.04 Gy), and for aligned-CT was (13.7 ± 4.80 Gy) (Figure 2), showing higher absolute differences in aligned-CT than in deformed-CT.

Relative percentage dose differences for target volumes DVH parameters between syn-CT and aligned-CT and syn-CT and deformed-CT for 10 patients were analyzed (Figure 3). The relative percentage dose difference (mean $\pm$ SD) values for deformed-CT, were (0.17 ± 0.33 %) for PTVEval $D_{98\%}$, (0.08 ± 0.27 %) for PTV $D_{98\%}$, and (0.07 ± 0.1 %) for CTV $D_{98\%}$. The relative percentage dose difference (mean $\pm$ SD) for aligned-CT, were (2.21 ± 2.46 %) for PTVEval $D_{98\%}$, (0.55 ± 0.65 %) for PTV $D_{98\%}$, and (0.09 ± 0.25 %) for CTV $D_{98\%}$.

Dosimetric DVH analysis for OARs such as Rectum and Bladder for a total of 10 patients were analyzed. Mean rectum DVH parameters $V_{70\text{Gy}}$, $V_{65\text{Gy}}$, $V_{50\text{Gy}}$ were (2.76 ± 4.01 %), (5.83 ± 5.94 %) and (11.6 ± 11.2 %), respectively for syn-CT, (1.37 ± 1.84 %), (4.02 ± 3.55 %) and (8.48 ± 6.67 %), respectively for aligned-CT and (3.23 ± 3.63 %), (5.60 ± 4.88 %) and (11.3 ± 8.18 %), respectively for deformed-CT. Results showed that DVH parameters are within our institutional guidelines, represented as dashed lines in Figure 4. Mean bladder DVH parameters $V_{70\text{Gy}}$, $V_{81\text{Gy}}$ were (3.41 ± 2.86 %), and (0.01 ± 0.01 cm³), respectively for syn-CT, (4.91 ± 3.65 %), and (0.20 ± 0.29 cm³), respectively for aligned-CT and (3.29 ± 2.76 %), and (0.1 ± 0.2 cm³) for deformed-CT (Figure 4), also within our institutional guidelines.

DVH analysis for OARs such as rectum and bladder were also done for spacer and non-spacer patients. Out of 10 patients there were 5 with spacer and 5 non-spacer. Rectum DVH parameters $V_{70\text{Gy}}$, $V_{65\text{Gy}}$, $V_{50\text{Gy}}$ for syn-CT spacer and non-spacer patients were as follows: (0.64 ± 0.72 %), (1.23 ± 1.19 %), (4.21 ± 2.81 %) and (4.89 ± 4.93 %), (10.4 ± 5.01 %),

(18.9 ± 11.7 %), respectively. Rectum $V_{70\text{Gy}}$, $V_{65\text{Gy}}$, $V_{50\text{Gy}}$ for aligned-CT spacer patients were (1.25 ± 1.95 %), (1.76 ± 2.59 %) and (4.00 ± 4.30 %), respectively and for aligned-CT non-spacer patients were (1.49 ± 1.94 %), (6.28 ± 3.00 %), (12.9 ± 5.59 %), respectively. On the deformed-CT Rectum $V_{70\text{Gy}}$, $V_{65\text{Gy}}$, $V_{50\text{Gy}}$ values were (0.87 ± 0.96 %), (1.60 ± 1.56 %), and (4.96 ± 3.17 %), respectively for spacer patients and (5.60 ± 3.84 %), (9.59 ± 3.34 %) and (17.6 ± 6.41 %), respectively for non-spacer patients. Bladder $V_{70\text{Gy}}$ for syn-CT, aligned-CT and deformed-CT were (4.81 ± 2.44 %), (6.69 ± 3.92 %), and (4.92 ± 2.55 %), respectively for spacer patients and (2.02 ± 2.75 %), (3.13 ± 2.59 %) and (1.66 ± 2.01 %), respectively for non-spacer patients. Bladder $V_{81\text{Gy}}$ for syn-CT, aligned-CT and deformed-CT were (0.01 ± 0.01 cm³), (0.22 ± 0.29 cm³), and (0.18 ± 0.23 cm³), respectively for spacer patients and (0.01 ± 0.01 cm³), (0.17 ± 0.32 cm³) and (0.02 ± 0.04 cm³), respectively for non-spacer patients (Figure 5).

Gamma analysis for all patients included in the study are shown in Table 2. The mean $\pm$ standard deviation value for a (2%, 2mm)_{10%} pass rate gamma analysis for the 10 patients included in the study were (99.5 ± 1.0 %) for deformed-CT, and (95.1 ± 6.8 %) for aligned-CT. Using a different dose cut off value of 50%, the (3%, 3mm)_{50%} pass rate gamma analysis for the deformed-CT and aligned-CT, were (99.9 ± 0.2 %) and (95.2 ± 5.7 %), respectively. On average higher pass rates were found on the deformed-CT than in the aligned-CT (Table 2).

4. Discussion

MR-only planning is the current standard for prostate photon treatment planning at our institution. In this study we have evaluated the feasibility of our institutional MR-only workflow for prostate on proton treatment planning. Our results showed that an MR-only workflow can be implemented in the clinical scenario using MR-derived synthetic CTs.

On average, the proton plans developed on the syn-CT showed higher absolute dose differences on aligned-CT as compared to deformed-CT. Dose differences on average were 14 Gy near bone/tissue abutting the PTV on aligned-CT due to inter-scan variabilities, resulting in different penetration depths for proton dose calculation, leading to underdose or overdose regions within the patient. Deformation of the aligned-CT to the syn-CT was a key factor to minimize inter-scan variabilities such as outer contour, internal organs position and air/bone discrepancies. Figure 6 shows the dose distribution of the absolute dose difference for representative patients with some of the variabilities mentioned before. Discrepancies in setup positioning can lead to outer contour variabilities, Figure 6a show setup uncertainties in a representative patient that can lead to 5 Gy on average of underdose or overdose areas within the patient. Deformation of the aligned-CT to the syn-CT minimized these discrepancies, although still leading to 3 Gy average dose differences areas within the patient.

In our institutional MR-only workflow three external MR-compatible radioopaque Beekley™ markers (BBs) are used to determine the plan isocenter by triangulating on these markers. These markers are positioned at right and left lateral and anterior to the patient. Since two beams at gantry angles of 90° and 270° were used for proton planning, two of the

three BBs were in the pathway of the beams leading to high dose uncertainties, these variabilities were not taken into account for our quantitative assessment of absolute dose differences within the patient, but they are represented in Figure 6b.

Proton planning is extremely sensitive to day-to-day setup uncertainties in femur angulation (Figure 6c). Both lateral beams pass through the high-density bones and result in dose differences of up to 17 Gy on aligned-CT and 5 Gy on deformed-CT, from femur angulation. Since prostate is matched based on implanted fiducial markers, position of femurs and the attenuation of beams through the bones must be carefully considered when implementing a fiducial based MR-only workflow for prostate using protons. In addition to patient setup uncertainties, some differences in absolute doses may also be arising from the fact that the treatment planning system uses a different calibration curve than the planning and synthetic CTs used here. Moyers has published on the variations between different CT scanners and the proton relative linear stopping power¹⁶. He found that variations between institutions were within $\pm 8\%$, hence the absolute values reported here could vary by that amount.

All the patients in this study had gold fiducials. Solid gold fiducials are not used clinically in protons because they would create shadows (cold spots) in the distribution¹⁷. Instead typically, coiled markers or carbon markers are used¹⁸. In this study, the fiducials were not overridden, but instead were left with their default HU which would mimic bone. The effect on the dose distribution is expected to be negligibly different. We spot-checked this by forcing the artifacts to and fiducials to unit density. Comparison with the syn-CT distributions, which do not result in higher HU units in the fiducials provides further evidence that the small HU changes could be ignored.

Percentage dose differences obtained for all DVH parameters on target volumes investigated were in the range of 0.07 % to 0.17 % for deformed-CT, and from 0.09 % to 2.21 % for aligned-CT, which are in good agreement with a previous study that showed the feasibility of MR-only proton planning. Koivula et al showed differences in target volumes for syn-CT relative to aligned-CT of 0.2% in brain and 0.1% in prostate cases¹³. Maspero et al, using the same commercial solution as this study but optimizing first on aligned-CT, obtained differences up to 15% for syn-CT with respect to aligned-CT in target volumes for prostate patients¹⁴. A previous study by Koivula et al showed no difference in dose comparison between syn-CT and aligned-CT when the optimization is performed first on aligned-CT or like in our study when the optimization is performed first on syn-CT¹³. The main differences observed in Maspero et al study was related to missing internal air cavities on the syn-CT¹⁴. Our institutional practice to insert hydrogel spacer into patients minimized this effect by moving away air pockets from the target volumes. On average, DVH parameters for target volumes were 2% higher in all image sets. Figure 5a shows DVH parameters for rectum in which $V_{65\text{Gy}}$ was lower in spacer patients for syn-CT, deformed-CT and aligned-CT. Spacer use is recommended to avoid air pockets close to the target and significantly decrease OARs DVH results and slightly improve dose coverage to the target. Additionally, the spacer will move air pockets away from the target if an syn-CT is used for optimization and dose calculation, however air pockets must be avoided when patients are simulated to avoid high dose discrepancies outside the target. Figure 6d shows an ideal case patient in which all

considerations have been taken into account, dose differences for deformed-CT were on average 2Gy.

Gamma analysis for all patients included in the study was above 95% for aligned-CT and deformed-CT, respectively. Our results using the most stringent gamma criteria, (2%, 2mm)10%, were $(99.5 \pm 1.0 \%)$ for deformed-CT, and $(95.1 \pm 6.8 \%)$ for aligned-CT, which were in agreement with previous studies by Koivula et al and Maspero et al^{13,14}.

Conclusion

Our dosimetric analysis shows that MR-only proton planning using syn-CT in the prostate is feasible. An MR-only workflow can be implemented in a clinical scenario taken into consideration clinical margins for targets that will account for range uncertainties.

Acknowledgments

This research was partially supported by the NIH/NCI Cancer Center Support Grant/Core Grant (P30 CA008748)

References

1. Rasch C, Steenbakkers R, van Herk M. Target definition in prostate, head, and neck. *Semin Radiat Oncol.* 2005;15(3):136–145. [PubMed: 15983939]
2. Nguyen PL, Aizer A, Assimos DG, et al. ACR Appropriateness Criteria(R) Definitive External-Beam Irradiation in stage T1 and T2 prostate cancer. *Am J Clin Oncol.* 2014;37(3):278–288. [PubMed: 25180754]
3. Prabhakar R, Haresh KP, Ganesh T, Joshi RC, Julka PK, Rath GK. Comparison of computed tomography and magnetic resonance based target volume in brain tumors. *J Cancer Res Ther.* 2007;3(2):121–123. [PubMed: 17998738]
4. Roberson PL, McLaughlin PW, Narayana V, Troyer S, Hixson GV, Kessler ML. Use and uncertainties of mutual information for computed tomography/ magnetic resonance (CT/MR) registration post permanent implant of the prostate [published online ahead of print 2005/03/26]. *Med Phys.* 2005;32(2):473–482. [PubMed: 15789594]
5. Nyholm T, Nyberg M, Karlsson MG, Karlsson M. Systematisation of spatial uncertainties for comparison between a MR and a CT-based radiotherapy workflow for prostate treatments [published online ahead of print 2009/11/19]. *Radiat Oncol.* 2009;4:54. [PubMed: 19919713]
6. Dowling JA, Sun J, Pichler P, et al. External Automatic Substitute Computed Tomography Generation and Contouring for Magnetic Resonance Imaging (MRI)-Alone Beam Radiation Therapy From Standard MRI Sequences [published online ahead of print 2015/11/20]. *Int J Radiat Oncol Biol Phys.* 2015;93(5):1144–1153. [PubMed: 26581150]
7. Tyagi N, Fontenla S, Zelefsky M, et al. Clinical workflow for MR-only simulation and planning in prostate [published online ahead of print 2017/07/19]. *Radiat Oncol.* 2017;12(1):119. [PubMed: 28716090]
8. Tyagi N, Fontenla S, Zhang J, et al. Dosimetric and workflow evaluation of first commercial synthetic CT software for clinical use in pelvis [published online ahead of print 2016/12/17]. *Phys Med Biol.* 2017;62(8):2961–2975. [PubMed: 27983520]
9. Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy [published online ahead of print 2014/06/17]. *Semin Radiat Oncol.* 2014;24(3):196–199. [PubMed: 24931092]
10. Legendijk JJ, Raaymakers BW, van Vulpen M. The magnetic resonance imaging-linac system [published online ahead of print 2014/06/17]. *Semin Radiat Oncol.* 2014;24(3):207–209. [PubMed: 24931095]

11. Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: clinical uses and future perspectives [published online ahead of print 2017/03/16]. *Nat Rev Clin Oncol*. 2017;14(8):483–495. [PubMed: 28290489]
12. Rank CM, Hunemohr N, Nagel AM, Rothke MC, Jakel O, Greilich S. MRI-based simulation of treatment plans for ion radiotherapy in the brain region. *Radiother Oncol*. 2013;109(3):414–418. [PubMed: 24268939]
13. Koivula L, Wee L, Korhonen J. Feasibility of MRI-only treatment planning for proton therapy in brain and prostate cancers: Dose calculation accuracy in substitute CT images. *Med Phys*. 2016;43(8):4634. [PubMed: 27487880]
14. Maspero M, van den Berg CAT, Landry G, et al. Feasibility of MR-only proton dose calculations for prostate cancer radiotherapy using a commercial pseudo-CT generation method. *Phys Med Biol*. 2017;62(24):9159–9176. [PubMed: 29076458]
15. Tang S, Deville C, McDonough J, et al. Effect of intrafraction prostate motion on proton pencil beam scanning delivery: a quantitative assessment [published online ahead of print 2013/08/21]. *Int J Radiat Oncol Biol Phys*. 2013;87(2):375–382. [PubMed: 23958148]
16. Moyers MF. Comparison of x ray computed tomography number to proton relative linear stopping power conversion functions using a standard phantom [published online ahead of print 2014/06/01]. *Med Phys*. 2014;41(6):061705. [PubMed: 24877800]
17. Giebler A, Fontenot J, Balter P, Ciangaru G, Zhu R, Newhauser W. Dose perturbations from implanted helical gold markers in proton therapy of prostate cancer [published online ahead of print 2009/02/19]. *J Appl Clin Med Phys*. 2009;10(1):2875. [PubMed: 19223836]
18. Cheung J, Kudchadker RJ, Zhu XR, Lee AK, Newhauser WD. Dose perturbations and image artifacts caused by carbon-coated ceramic and stainless steel fiducials used in proton therapy for prostate cancer [published online ahead of print 2010/11/16]. *Phys Med Biol*. 2010;55(23):7135–7147. [PubMed: 21076190]

Figure 1:
Hounsfield unit histograms extracted from aligned-CT scan for Soft Bone, Cortical Bone, Fat, and Muscle.

Figure 2:
Boxplot representing the absolute max dose differences computed in the inner body volume between aligned-CT and deformed-CT with respect to syn-CT respectively for all patients.

Figure 3:
Boxplots representing the relative percentage dose differences for PTVEval D_{98%} and CTV D_{98%} between deformed-CT (a) and aligned-CT (b) in respect to syn-CT for all patients.

Figure 4:

Boxplots representing Rectum V_{70Gy}, V_{50Gy} and Bladder V_{70Gy} for syn-CT, aligned-CT and deformed-CT, respectively in all patients. Our institutional guidelines are represented with dashed lines for each organ and DVH parameter.

Figure 5: Boxplots representing DVH parameter V_{65Gy} for rectum (a) and V_{70Gy} Bladder (b) by patient group, spacer and non-spacer for syn-CT, deformed-CT and aligned-CT, respectively. Our institutional guidelines are represented with dashed lines for each organ and DVH parameter.

Figure 6:

Dose difference distribution on deformed-CT and aligned-CT in four representative patients.

A) Non-Spacer patient with high dose differences on aligned-CT due to Setup uncertainty.

B) Patient with spacer reflecting the effect of BBs on dose calculation. C) Non-Spacer

patient with bone/air uncertainties. D) Ideal spacer patient in which uncertainties were

minimized offering good dose agreement between deformed-CT aligned-CT and syn-CT.

Table1.

Patient characteristics

Patient characteristics	n (%)
Age (years)	72.5 ± 10 years (range 52–85 years)
Gleason Score	
3+4	5 (50%)
4+3	2 (20%)
4+4	1 (10%)
4+5	2 (20%)
Risk Group	
Low	0 (0%)
Intermediate	7 (70%)
High	3 (30%)
Clinical or Pathological T stage	
Tx	1 (10%)
cT1a	0 (0%)
cT1b	0 (0%)
cT1c	4 (40%)
cT2a	3 (30%)
cT2b	1 (10%)
pT3b	1 (10%)
Hydrogel (Spacer)	
Yes	5 (50%)
No	5 (50%)
Radiation Therapy Technique	Pencil Beam Scanning (PBS) Proton Therapy
Dose (Gy (RBE))	68.4 – 79.2
Fractions	38 – 44

Table 2.

Dose distribution comparison of PBS plans on aligned-CT and deformed-CT using gamma criteria with different dose cutoffs. Percentage pass rates for each patient and average and standard deviation (SD) are given.

#Patient	aligned-CT		deformed-CT	
	(3%, 3 mm)50%	(2%, 2 mm)10%	(3%, 3mm)50%	(2%, 2 mm)10%
1	100	100	100	100
2	100	99.9	100	100
3	100	99.9	100	99.7
4	85.6	89.7	100	100
5	93.5	96	100	100
6	92.5	95.5	99.3	98.6
7	86.6	78.3	100	99.9
8	93.4	94.3	100	100
9	100	100	100	99.9
10	100	97.4	99.9	97.1
Average	95.2	95.1	99.9	99.5
SD	5.7	7.7	0.2	1.0