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Dose deformation-invariance in adaptive prostate radiation therapy: implication for treatment simulations

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Abstract

Purpose—To investigate dose deformation-invariance in adaptive prostate radiation treatment.

Methods—A nineteen patient prostate cancer-cohort with 8-13 CTs/patient is used. The 79.2 Gy plans are developed on the reference image using seven 6 MV and 18 MV intensity-modulated beams with identical RTOG 0126 objectives. Dose on the subsequent images is evaluated in two ways: (A1) Dose is recalculated on each image. (A2) The initially planned dose distribution is copied to each image. A2 assumes dose-invariance in the accelerator-coordinate-system. Effects of patient miss-alignment are simulated by 27 per-patient image shifts; 0 and ± 10 mm in left-right, anterior-posterior and superior-inferior directions. The per-voxel dose differences for each patient image, total accumulated patient dose, and dose-volume metrics (CTV-D98 and -D90, bladder- and rectum-D50, -D35, -D25 and -D15) are used to compare A1 and A2.

Results—The per-voxel mean percent difference in A1 and A2 dose over all patient images at 6 MV is (0.01 ± 1.56) % and at 18 MV is (0.00 ± 0.96) %. For 6 MV and 18 MV plans, the root-mean-square-percentage-error (RMSPE) in A2 over all patient image shifts are CTV-D98 = 0.94 and 0.55, CTV-D90 = 0.92 and 0.55 rectum-D50, -D35, -D25 and -D15 = 1.00, 0.96, 0.86, 0.80 and 0.84, 0.96, 0.92, 1.05; and bladder-D50, -D35, -D25, -D15 = 1.07, 0.88, 0.78, 0.72 and 1.61, 0.93, 0.67, 0.51. The dose differences are not correlated to the dice-similarity coefficients; with respective correlation-coefficients for CTV, rectum and bladder being -0.17 , -0.17 and 0.081 .

Conclusions—Assumption of shift- and deformation-invariant dose distributions on an average introduces $<2\%$ error in evaluated dose-volume metrics for 6 MV and 18 MV IMRT prostate plans. Use of invariant dose distributions has a potential to reduce online re-planning time and permit pre-planning based on tissue deformation models.

Keywords

Adaptive radiation treatment; prostate; deformation-invariance; shift-invariance

1 Introduction

Repeated patient imaging via fan-beam CT (FBCT) and cone-beam CT (CBCT) demonstrates that daily patient alignment and internal organ shapes change during the course of prostate radiation treatment. The clinical effect of radiation delivery to changing patient anatomy can be estimated from the cumulative dose delivered, which is obtained by deformably mapping and summing dose computed on each patient image to a reference image. In image guided radiation treatment (IGRT), time-of-treatment adaptation decisions can be made based on the accumulated dose-to-date plus the estimated dose delivery for the treatment day. However, the combined time-consuming aspects of daily imaging, dose computation, and plan re-optimization limit the practicality of on-line adaptation.

In addition to or as an alternative to image guidance, treatment plans can be designed to be robust to patient setup uncertainties and organ-deformations. Analysis of patient images have shown that the prostate, rectum and bladder deformations can be modeled using principal-components analysis [1,2], which permits creation of multiple probable pseudo-patient anatomies. In probabilistic and coverage-optimized robust planning techniques [3,4], one simultaneously optimizes over multiple probable instances of the patient's anatomy. This requires dose evaluation for each organ deformation state. Due to the prohibitively large time required by repetitive dose calculations during probabilistic plan creation, probabilistic methods developed to date are limited to models which assume rigid tissue motion, whereas convolution [5] and resampling techniques [6] assume dose-invariance to translational anatomic shifts. While shift-invariance permits use of a single dose computation for dose evaluations on all anatomic states, the simplistic rigid tissue model limits the clinical applicability of probabilistic planning models.

The present study aims to determine the validity of using shift- and deformation-invariance for prostate treatment dose evaluations. A shift- and deformation-invariant dose distribution implies that the dose distribution in an accelerator-coordinate-system does not vary as the patient anatomy changes its position and/or deforms within that coordinate system. The shift- and deformation-invariance will have a proximate implication in IGRT where the 4D dose is summed over multiple anatomies, which normally entails dose computation on each anatomy followed by deformable dose mapping and summation. If shift and dose-invariance are shown to be valid in the accelerator-coordinate-system, the 4D dose summation is simplified to a single dose computation, followed by multiple deformable dose mappings and summation to a single image. Moreover, invariant dose will enable the use of deformable models in probabilistic plan creation within clinically acceptable time.

Prostate anatomies are generally deformed due to volumetric changes and effects of rectal and/or bladder filling [7,8]. The dosimetric consequences of prostate motion [9] and effect of shift-invariance [10] on modeling dosimetric uncertainties have been investigated. But, the effect of shifts on non-rigid tissue deformations has never been demonstrated. The purpose of this study is to (a) determine validity of shift- and deformation-invariance, and (b) to test if shift- and deformation-invariance are related to the extent of deformations in prostate anatomies. Simulations with shifted and deformed anatomies respectively imitate the daily setup errors and deformations in patient's anatomy during the course of IGRT. The shift- and

deformation-invariance is tested at two clinically used IMRT beam qualities viz. 6 MV and 18 MV. The authors find this to be the first systematic analysis of impact of clinically relevant shifts and deformations on the dose estimations.

2 Methods and materials

2.1 Patient Data

Images obtained from a 19-prostate cancer patient-cohort from the Netherlands Cancer Institute (NKI) are used in this study. The details of patient disease stage and planning CT protocol are described elsewhere [11]. Each patient was treated in supine position and has multiple (8-13) FBCT images taken during a 7-8 week course of conformal radiotherapy. The boney-anatomy aligned FBCT images with ~70 (66-77) slices are resampled to have 3 mm slice thickness, and have 512×512 image resolution. For planning purposes, the first image is imported as reference image (S0). The remaining images are imported as secondary images and are named as Si where “i” is the sequence number of collection e.g. S1 (i = 1) corresponds to the 1st “treatment” image acquired. For each patient image, the following structures are delineated by a single physician: prostate, seminal vesicles, rectum, bladder, left femur and right femur.

2.2 IMRT planning on S0

The physician-delineated CTV includes prostate and seminal vesicles. The original plans used for treatment were not available; as such, this retrospective study simulated a virtual treatment. The treatment plan optimization objectives and dose criteria are modeled according to high dose arm of the Radiation Therapy Oncology Group (RTOG) protocol 0126. The objectives include dose volume histogram (DVH) requirements for the PTV (CTV with 5 mm margin), bladder, rectum, right femur and left femur. For each patient, independent IMRT treatment plans are created with photon beam qualities of 6 MV and 18 MV. Seven beams at gantry angles of 30°, 80°, 130°, 180°, 230°, 280° and 330° and direct machine parameter optimization (DMPO) algorithm are used to generate IMRT treatment plans on S0 using Pinnacle³ (Version 9.100) treatment planning system (Philips Medical Systems, Fitchburg WI). A 2×2×2 mm³ dose-grid is used in conjunction with an adaptive convolution algorithm for all dose computations. This algorithm is suggested by AAPM Task Group No. 65 [12] in presence of inhomogeneities. With the present work being a comparison study, further details of the treatment planning process are not explained.

2.3 Shift- and deformation-invariance

To validate shift- and deformation-invariance on each subsequent i^{th} image, a T_{Si} image-set trial is created in Pinnacle³. Based on the available CT images, i varies from 8-13. Initial 6 MV and 18 MV IMRT treatment plans are created on the reference image-set trial T_{S0} . After beam optimization, the prescription in T_{S0} is translated to monitor units. For each of the 227 patient images, 27 patient-shifts are defined from all possible combinations of 0 and ± 10 mm in left-right, anterior-posterior and superior-inferior directions. The minimum shift is 0 mm (0 mm, 0 mm, 0 mm) and the maximum shift is 17 mm (± 10 mm, ± 10 mm, ± 10 mm). A 10 mm shift increment is chosen since it is twice the CTV-to-PTV margin and is larger than anticipated patient offsets. As outlined in Fig. 1, for each shift two arms (A1 and A2) are

used to evaluate dose for each $T_{Si}^{(l=0)}$ image-set. In Step I, the beam parameters and original monitor units of T_{S0} are copied to the T_{Si}^{th} image-set trial in A1, while in A2 dose is directly copied to T_{Si}^{th} image-set trial. A2 assumes dose to be fixed in the accelerator-coordinate-system, independent of the image of the day (deformation-invariance) and independent of the patient setup-error (shift-invariance). In Step II, dose in A1 is recomputed with no optimization (A2 does not require recomputation). Step III accumulates dose from all T_{Si} 's to T_{S0} . The Pinnacle³ (v 9.100) based demons deformable registration algorithm is used for dose mapping and accumulation. After each deformation (Step I) and shift (Step II), A1 and A2 per-voxel dose and dose-volume metrics are compared for each T^{th} S_i image-set trial (Fig. 1, red arrows) and the accumulated dose trial (Fig. 1, blue arrows). Fig. 2 demonstrates A1 and A2 for a 10 mm shift.

2.4 Evaluation methods

For each patient image shift, differences in per-voxel dose and dose-volume metrics viz. CTV-D98, -D90, rectum- and bladder-D50, -D35, -D25 and -D15 and cumulative dose volume histograms (DVH) are compared for the two arms.

For a particular shift, T_{Si}^{th} image-set trials in A1 and A2 have a different dose-grid origin, hence, the per-voxel dose differences are determined after interpolating the dose-grid in A2 to co-ordinates in A1. This is done using the 3D linear interpolation method ("interp3" routine in MATLAB). The voxels containing air have dose set to zero to mimic the dose calculation algorithm behavior. A dose-difference probability distribution is created from the percent dose difference histograms normalized to the prescription dose for all patient image shifts.

The dose metrics are compared for all T_{Si} 's in an individual patient and for all T_{Si} 's in all the patients together in terms of the root-mean-square-percent-error (RMSPE) in absolute dose values by the relation

$$RMSPE = \sqrt{\sum_{T_{Si}} \left(\frac{D_m^{T_{Si}}(A1) - D_m^{T_{Si}}(A2)}{D_m^{T_{Si}}(A1)} \right)^2} \quad (1)$$

Where, $D_m^{T_{Si}}(A1)$ and $D_m^{T_{Si}}(A2)$ respectively represent dose metric values ($m=98, 90$ for prostate and $m=50, 35, 25$ and 15 for rectum and bladder) in A1 and A2. For a T_{Si}^{th} image-set trial of an individual patient $D_m^{T_{Si}}$ represents dose received by $m\%$ of the indicated structure.

The anatomical variations in shape or volume of prostate, rectum and bladder are ascertained from the dice similarity coefficient (DSC) [13]. For a given structure, DSC indicates volume overlap ratio of the structure in $S0$ and S_i image. The DSC is calculated as

$$DSC(V_{S0}, V_{Si}) = \frac{2 |V_{S0} \cap V_{Si}|}{|V_{S0}| + |V_{Si}|} \quad (2)$$

Where, for a given structure, V_{S0} and V_{Si} are the volumes (cm^3) in $S0$ and Si image. The DSC approaches 1 when there is perfect overlap and 0 when there is no overlap in the two images. In other words, the smaller the value of DSC, the larger is deformation in that structure.

3 Results

The extent of deformation in different treatment day anatomies is accessed by the maximum centroid motion statistic and DSC values. The images used in the study are boney-anatomy aligned. The maximum centroid motion for prostate and bladder respectively is 4.5 mm and 10.7 mm in anterior-posterior (Y) direction and for rectum is 7.7 mm in superior-inferior (Z) direction. The mean and standard deviation in DSC values of the 227 images with respect to their reference images are 0.76 ± 0.14 , 0.71 ± 0.14 and 0.67 ± 0.12 for CTV, rectum and bladder respectively. Large bladder deformations are due to differential bladder filling on different treatment days. The patients followed pre-treatment and pre-scan empty bladder and rectum protocol [11]. Variations in bladder volume even after following such protocols is a common observation [14].

Sample PTV, rectum and bladder cumulative DVHs for A1 and A2 are shown in Fig. 2. Fig. 3 shows per-image trial and per-accumulated dose trial percentage-difference in dose-volume metric values in A1 and A2. Each black histogram-bar represents the average over 27 shifts for a given image trial while the red bar represents the percentage-difference in the dose accumulated from all trials in a patient. The dose invariance assumption seems to overestimate prostate D98 but most of the percentage-differences are $< 2\%$. Appendix A shows the RMSPE of the 27 patient shifts for the rectum and bladder dose-volume metrics 6 MV and 18 MV. The only RMSPE values $> 2\%$ are at 18 MV Patient_2 bladder results (3.8% D50, 2.35% D35) and Patient_3 bladder D50 results at 6 and 18 MV (2.94% and 4.5% respectively). The dice similarity coefficients showed greater degree of overlap between PTV and bladder in case of Patient_2 and Patient_3.

Fig. 4 shows differential and cumulative probability distributions of normalized percent dose difference between A1 and A2 for all voxels in the dose volume. The mean percent difference and standard deviation at 6 MV ($0.01 \pm 1.56\%$) is larger than at 18 MV ($0.00 \pm 0.96\%$).

While DSC values range from 0.1 to 1.0, the percentage-difference between A1 and A2 dose-volume metrics (Fig. 5) vary randomly in a $\pm 2\%$ range. Correlation coefficients (r) values for CTV, rectum and bladder are -0.17 , -0.17 and 0.081 , indicating a lack of correlation between percentage-error between A1 and A2 dose-volume metrics and DSC values or organ deformations. Similarly, insignificant correlation is found between the A1 and A2 dose volume metrics and the shift distances (10, 14, and 17 mm).

4 Discussion

This study establishes the dose deformation-invariance for prostate therapy. The dose-invariance is found to be simultaneously valid for set-up errors, inter-fractional deformations in anatomies and for full dose accumulation with each fraction based on the CT images taken during the course of radiation treatment. The per-voxel dose differences, different comparison metrics and DVHs support equivalence in A1 and A2.

IGRT typically uses FBCT for an initial treatment planning and CBCT to monitor or adapt to daily anatomical changes. There is an inherent error involved in translating from Hounsfield units (HUs) to electron density of CBCT [15]. The existence of dose deformation-invariance when doing deformable dose mapping and summation based single reference image (S0) justifies using the planning CT image with CBCT contours for time-of-treatment dose calculation (during adaptive planning). This circumvents the problem with CBCT HU to density conversion.

Internal organ motion including variable bladder and rectal filling [7,9], and variations in seminal vesicles and prostate [11] leads to daily changes in prostate localization. Moreover, there may be some inaccuracies pertaining to manual delineations which, in turn, affect dose delivery accuracy. The present study demonstrates that volume overlap discrepancies calculated with per-patient image DSC values are not correlated with percentage-differences in dose-volume metrics between A1 and A2.

A recent statistical study on interfraction prostate motion and deformation and their dosimetric effects showed negligible deformation and rotation in ~70% of treatment fractions while ~30% of fractions would benefit from online replanning [7]. While dose deformation-invariance holds promise to speed up adaptive replanning processes, considerable time is still spent on dose re-optimization. An alternative to online replanning is to *a priori* create multiple virtual clinical plans with most probable deformations in the patient's anatomy and setup-errors that might exist during the course of treatment. This may substantially reduce the treatment planning time from optimizing on each treatment fraction to few treatment fractions with large deformations. With dose being invariant to the internal organ deformation state, principal-components analysis models which simulate the internal organ motions will be sufficient for an alternative treatment plan creation.

Dose deformation-invariance permits rapid evaluation of target coverage probabilities for target-coverage evaluation [3] or probabilistic treatment planning [4] provided a model of patient organ deformations exists. The time required to compute dose for multiple anatomic instances can be saved by copying dose from the planning image to different daily patient anatomies.

The effect of different image registration algorithms used on the accuracy of accumulated dose is a current area of research. In a recent phantom and single patient study, the two non-rigid registration methods (Demons and Morphons) used for dose accumulation [16] were found equivalent. As both A1 and A2 use the same demons algorithm for dose accumulation, the effect of inherent uncertainties in the dose accumulation algorithms has no effect on the results of this study.

It should be noted that dose deformation-invariance findings may depend on the dose-grid resolution. In the present study a dose-grid resolution of 2 mm is used. When insufficient dose-grid resolution is used, DVH evaluated metrics depend upon the dose-grid origin due to interpolation errors in adjacent voxels. For a head-and-neck phantom study, Chung *et.al.* [17] found shifting the calculation dose-grid origin by half a voxel resulted in dose differences of 1.9%, 2.8% and 3.8% for dose-grid resolutions of 2, 3 and 4 mm respectively. In preliminary data acquisition for this study, we observed discrepancies/ambiguities between A1 and A2 in 4 out of 19 patient bladder anatomies with 4 mm dose-grid resolution which were resolved when we used 2 mm dose-grid resolution.

With proper consideration of dose-grid resolution and within clinically relevant shifts and deformations, the dose distributions in prostate can be considered to be shift- and deformation-invariant. This has a strong potential in adaptive prostate treatment as an *a priori* simulation of different day treatment can be done offline to create multiple virtual plans comparable to an online reoptimization process. The time-of-treatment IGART dose calculations can be replaced with simple dose evaluation based on the planned dose distribution overlaid on the time-of-treatment patient image-without the need to transfer data to the treatment planning system. This could be done by a record and verify system.

5 Conclusions

The present work has determined the existence of dose shift- and deformation-invariance in radiation treatment planning of prostate cancer. This study is a baseline validation study which enables development of alternative offline adaptive strategies. Dose deformation-invariance permits rapid evaluation of target coverage probabilities or probabilistic treatment planning provided a model of patient organ deformations exists. In this paper, we concentrate on adaptive radiation therapy. The results of this study are important even for non-adaptive radiation therapy where dose is summed over multiple images. Similar studies should/will be done in other types of cancer such as head and neck and lung cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

The RMSPE in 27 dose-volume metrics of rectum and bladder for 19 patients for 6 MV and 18 MV delivery. For a given patient, the value represents the dose-volume metrics RMSPE averaged over $[(8 \rightarrow 13) * 27]$ shifts, where $8 \rightarrow 13$ represents the available CTs/patient.

Patient	Energy	Root Mean Square Percent Error (RMSPE)							
		Rectum				Bladder			
		D50	D35	D25	D15	D50	D35	D25	D15
Patient_1	6 MV	1.50	1.14	0.95	0.74	0.92	0.72	0.39	0.41
	18MV	0.79	0.54	0.53	0.55	0.43	0.36	0.29	0.55
Patient_2	6 MV	1.06	1.11	0.84	0.81	0.67	0.51	0.91	1.14
	18MV	1.29	1.61	1.16	1.17	3.80	2.35	1.32	1.17
Patient_3	6 MV	0.36	0.34	0.33	0.30	2.94	1.61	1.06	0.62
	18MV	0.27	0.23	0.24	0.27	4.53	1.86	0.82	0.27
Patient_4	6 MV	1.00	0.57	0.53	0.51	0.65	0.65	0.69	0.75
	18MV	0.50	0.95	1.31	1.47	0.49	0.49	0.46	1.47
Patient_5	6 MV	0.55	0.56	0.60	0.67	0.49	0.53	0.55	0.50
	18MV	0.34	0.34	0.38	0.43	0.25	0.28	0.29	0.43
Patient_6	6 MV	0.69	0.55	0.59	0.73	1.56	1.65	1.29	1.19
	18MV	0.88	0.90	0.92	0.94	1.90	1.57	1.41	0.94
Patient_7	6 MV	1.25	0.80	0.79	0.76	0.56	0.79	0.54	0.36
	18MV	1.30	0.71	0.65	0.72	0.63	0.76	0.66	0.72
Patient_8	6 MV	0.41	0.37	0.36	0.28	0.52	0.66	0.91	0.43
	18MV	1.11	1.98	1.07	1.12	0.71	0.81	0.95	1.12
Patient_9	6 MV	1.20	0.83	0.76	0.78	1.44	1.46	1.10	0.87
	18MV	0.90	0.66	0.88	1.47	1.06	0.54	0.63	1.47
Patient_10	6 MV	1.11	0.91	0.92	0.96	0.74	0.73	0.75	0.87
	18MV	0.48	0.82	1.28	1.68	0.33	0.37	0.43	1.68
Patient_11	6 MV	0.83	0.78	0.81	0.85	0.67	0.78	0.82	0.84
	18MV	1.22	0.43	0.41	0.52	0.45	0.49	0.48	0.52
Patient_12	6 MV	1.23	1.21	1.21	1.26	0.92	0.90	0.90	0.90
	18MV	0.66	0.91	0.53	1.28	1.10	0.66	0.53	1.28
Patient_13	6 MV	0.48	0.51	0.69	0.85	0.67	0.56	0.43	0.44
	18MV	0.69	0.88	1.06	1.20	0.84	0.63	0.53	1.20
Patient_14	6 MV	0.94	0.82	0.66	0.63	0.50	0.48	0.46	0.45
	18MV	0.64	0.59	0.57	0.58	0.64	0.46	0.42	0.58
Patient_15	6 MV	1.47	1.31	1.20	1.14	0.74	0.66	0.67	0.72
	18MV	0.87	0.72	0.65	0.61	0.51	0.47	0.44	0.61
Patient_16	6 MV	0.55	0.75	0.90	0.94	1.00	0.74	0.65	0.63
	18MV	0.81	1.08	1.22	1.21	0.78	0.39	0.37	1.21
Patient_17	6 MV	1.24	0.98	0.86	0.78	0.58	0.58	0.49	0.40
	18MV	0.84	0.69	0.66	0.70	1.18	0.64	0.47	0.70
Patient_18	6 MV	1.29	0.96	0.71	0.49	0.64	0.48	0.46	0.52
	18MV	0.72	0.80	1.12	1.37	0.65	0.28	0.30	1.37
Patient_19	6 MV	0.92	1.21	1.37	1.34	0.92	0.90	0.95	0.89
	18MV	0.63	1.22	1.18	0.99	0.65	0.87	0.79	0.99

7 References

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Fig. 1.
Schematic representation of A1 and A2 methodology used for each patient image shift to study the validity of shift- and deformation-invariance.

Fig. 2.

A pictorial comparison of A1 and A2 dose evaluation methods. The dose distribution is shown as a color wash. Prostate (red), bladder (black), and rectum (magenta) contours are indicated on images. (a) Shows the original dose distribution. (b) Shows the dose in (a) with beam outlines, and the isocenter from (a) is shifted laterally by 10 mm and dose is recomputed. (c) Shows the A2 dose, which is the dose matrix from (a) shifted laterally by 10 mm. The difference in dose-volume metrics from (b) and (c) are used to evaluate the dose error introduced by assuming A2 dose-invariance. (d) CTV, rectum and bladder cumulative DVH's from A1 and A2 in 9 out of 19 Patients at 18 MV.

Fig. 3.

Per-image percentage difference in CTV-D98 and -D90, rectum- and bladder-D25 values calculated in A1 and A2 at (a) 6 MV and (b) 18 MV. The mean (μ) and standard deviation (σ) are reported at the bottom of each plot. Horizontal axis represents patient number. Each black bar represents an average over 27 shifts for a given image-set trial T_{Si} , where maximum value of i varies from 8-13 depending upon the available number of patient images. The red bar represents the average over 27 shifts for the accumulated dose.

Fig. 4. Probability distribution (top) and cumulative probability distribution (bottom) of per-voxel percent dose difference at 6 MV and 18 MV in all patient shifts in A1 and A2

Fig. 5. Scatter plot between DSC and percentage-differences in dose-volume metrics (CTV-D90, rectum- and bladder-D25).