Multileaf Collimator Tracking Improves Dose Delivery for Prostate Cancer Radiation Therapy: Results of the First Clinical Trial

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Summary

Multileaf collimator tracking has been implemented for the first time in a prospective prostate cancer clinical trial. Dose reconstruction was performed for 475 treatment fractions for 15 patients.

Comparison of patients' original planned dose with the calculated treated dose with and without MLC tracking demonstrates that implementation of MLC tracking results in a higher agreement between delivered and planned doses. The implications are potentially improved patient outcomes and more reliable radiobiological parameter determination.

Abstract

Purpose: To test the hypothesis that multileaf collimator (MLC) tracking improves the consistency between the planned and delivered dose compared with the dose without MLC tracking, in the setting of a prostate cancer volumetric modulated arc therapy trial.

Methods and Materials: Multileaf collimator tracking was implemented for 15 patients in a prostate cancer radiation therapy trial; in total, 513 treatment fractions were delivered. During each treatment fraction, the prostate trajectory and treatment MLC positions were collected. These data were used as input for dose reconstruction (multiple isocenter shift method) to calculate the treated dose (with MLC tracking) and the dose that would have been delivered had MLC tracking not been applied (without MLC tracking). The percentage difference from planned for target and normal tissue dose-volume points were calculated. The hypothesis was tested for each dose-volume value via analysis of variance using the *F* test.

Results: Of the 513 fractions delivered, 475 (93%) were suitable for analysis. The mean difference and standard deviation between the planned and treated MLC tracking doses and the planned and without-MLC tracking doses for all 475 fractions were, respectively, PTV $D_{99\%}$ −0.8% ± 1.1% versus −2.1% ± 2.7%; CTV $D_{99\%}$ −0.6% ± 0.8% versus −0.6% ± 1.1%; rectum $V_{65\%}$ 1.6% ± 7.9% versus −1.2% ± 18%; and bladder $V_{65\%}$ 0.5% ± 4.4% versus −0.0% ± 9.2% (P<.001 for all dose-volume results).

Conclusion: This study shows that MLC tracking improves the consistency between the planned and delivered doses compared with the modeled doses without MLC tracking. The implications of this finding are potentially improved patient outcomes, as well as more reliable dose-volume data for radiobiological parameter determination.

Introduction

Dynamic multileaf collimator (MLC) tracking has been developed as a real-time adaption technique for improving the accuracy of radiation therapy treatment delivery and has undergone extensive preclinical development (1). Aspects of the development have included assessment of the geometric (2) and dosimetric accuracy, quality assurance processes (3), and compatibility with Varian (2), Elekta (4), and Siemens (5) treatment machines. Multileaf collimator tracking has been developed for use with different treatment techniques, such as intensity modulated radiation therapy (6) and volumetric modulated arc therapy (VMAT) (7), and with various tumor localization systems, including megavoltage imaging (8), kilovoltage (kV) imaging (9), and electromagnetic transponder tracking (10).

A requirement for the clinical implementation of MLC tracking is an integrated real-time tumor localization system. One of these systems routinely used for observation of the prostate position during treatment is the Calypso electromagnetic transponder tracking system (Varian Medical Systems). Many of the preclinical MLC tracking studies to date involved the integration and development of the Varian Calypso localization system with the real-time MLC tracking system (6, 10).

Application of real-time adaptation necessitates innovative solutions for treatment delivery validation, and dose reconstruction methods have been developed to be used as a posttreatment quality assurance step for clinical implementation of MLC tracking (11, 12). Dose reconstruction techniques allow the calculation of dose after each treatment fraction to provide an estimate of the treated dose delivered to the patient. In this study, dose reconstruction was performed for the majority of fractions for 15 patients on the first prospective clinical MLC tracking trial. The reconstructed doses were used to test the hypothesis that MLC tracking improved the agreement between the planned and delivered doses for prostate cancer radiation therapy treatments.

Methods and Materials

The ethics, governance, legal, and regulatory processes were completed before the initiation of the clinical trial. Ethical and regulatory approval (Australian Therapeutic Goods Administration) was established for the use of Calypso Research Mode (Varian Medical Systems).

Clinical trial

The first prospective clinical trial implementing Calypso- guided MLC tracking commenced in November 2013 (NCT02033343) (13). The primary endpoint of the prostate trial was the successful implementation of MLC tracking for at least 95% of all fractions. Secondary endpoints include the assessment of the delivered dose and modeling of radiobiological effects. Patients eligible for the trial were those undergoing external beam radiation therapy for histologically proven prostate adenocarcinoma, with and without nodal dose coverage and prostate gross tumor volume (GTV) (defined by MRI, clinical examination, and biopsy positivity). The patient also had to meet the body habitus criteria for the use of the Varian Calypso system for tracking and to be able to have the Calypso beacons placed in the prostate. All patients gave written consent to participate in the study.

The characteristics of the 15 patients are shown in Table 1. There were 2 main treatment fractionation schedules used for the trial. Five patients received the conventional fractionation schedule of 80 Gy in 40 fractions, with 95% of the prescribed dose to be delivered to 100% of the planning target volume (PTV). Any defined GTVs were allowed to receive 110% of the prescribed dose.

Six patients were selected to receive the second fractionation schedule, designed to mimic high-dose-rate brachytherapy boost followed by external beam radiation therapy. The patients received 2 10-Gy boost fractions 1 week apart, followed by 46 Gy delivered in daily 2-Gy fractions. The prescription for the boost part was a PTV V_{20Gy} of at least 95%, and any defined GTV was prescribed 25 Gy. All patients were planned for the boost, with a catheter in situ. The catheter with a 2-mm margin was limited to receive 5% of the prescription dose to 100% of the volume and 50% of the urethra to receive <18 Gy.

Two of the first 15 patients received altered fractionation schedules. One patient, after receiving 1 fraction of 10 Gy, experienced urinary retention, a grade 3 complication, and for this reason the second 10-Gy fraction was not delivered, and the remainder of his treatment was changed to 60 Gy in 30 fractions. Another patient on the boost fractionation schedule was diagnosed with an unrelated condition requiring him to finish treatment early. For this reason the patient fractionation schedule changed to 20 Gy in 2 fractions, 32 Gy in 16 fractions, and 12 Gy in 4 fractions.

Planning and treatment

Planning

All MLC tracking treatments were planned using Eclipse 11.1.47 (Varian Medical Systems) for delivery on a Varian Trilogy linear accelerator with Millenium120 MLC. The

plans were dual arc VMAT 6-MV photons. The margins for the standard 2-Gy fractions were not changed from the regular standard margins of 7 mm with 5 mm posterior. Margins for the fractions of 10 Gy were 5 mm with 3 mm posterior. Once plans were completed to fit dose constraints and prescriptions, alterations were made to the plans to allow the implementation of MLC tracking. Each of the collimator jaws were opened a further 8 mm to allow the real-time movement of the MLC aperture without moving beneath the collimator jaws. To account for this extra area, the plan was renormalized and the coverage and dose constraints reassessed. A copy of the MLC file was created for each treatment arc; the files contain MLC positions as a function of gantry angle along with patient identifiers and were used as input into the MLC tracking software at the time of treatment. Once all alterations were made, the planned dose was again assessed and patient-specific quality assurance (portal dose delivery with and without MLC tracking with zero motion file) was performed.

Setup and treatment

Patients were positioned and set up using the Calypso localization system, and for the 2-Gy fractions standard kV/ kV or cone beam computed tomography (CBCT) were not routinely acquired. For the fractions of 10 Gy, the patients received an enema 1 hour before treatment, and 5 of the 6 patients who received boost fractions were catheterized for these deliveries. The patients were set up with Calypso, and a CBCT was then obtained and compared with the Calypso information by a clinician at the treatment console. The urethral and target positions were checked, and the treatment was approved by the physician. At setup, if the target rotation was greater than 10^{o}, a CBCT was obtained and an assessment performed using an overlay of the planned structures to ensure the prostate was within the target volume before beginning treatment.

Once the patient was set up and the treatment field was ready, the MLC tracking software was connected. The software had input of the real-time Calypso position (research mode) information and the treatment field MLC file obtained from the patients' treatment plan containing all MLC positions in respect to gantry angle. Once the MLC tracking software was connected, it assumed control over the MLC controller and, by combining the planned MLC positions with the real-time location of the target, calculated new MLC positions and continually sent these to the treatment machine.

Before each treatment arc the motion of the prostate was assessed, and if the displacement was >2.5 mm in any direction, a couch shift was applied from Calypso to return the target to the planned position. During the treatment arcs, a beam hold results when displacement of the target exceeds 8 mm in any of the 3 patient dimensions (via Calypso) or in the beams-eye view (via MLC tracking). If the excursion was persistent, the couch would be shifted to return the target to the planned position and the treatment resumed.

Data collected during the treatment include the Calypso observed prostate motion trajectory and the treatment machine log files, which contain the treatment MLC positions as well as gantry and dose information.

Dose reconstruction

After each treatment fraction, an isocenter shift dose reconstruction method (12) was used to determine the treated dose delivered to the patient with MLC tracking and the modeled dose that would have been delivered without MLC tracking (Fig. 1). The plan corresponding to the treated dose (with MLC tracking) was created using an in- house MATLAB (R2013b) program by combining the patient's original treatment plan and dose with the observed prostate motion (translation only) and the treatment MLC positions collected during the fraction delivery. This treatment plan was then imported into the treatment planning system (Eclipse 11.1.47) and treated dose calculated for comparison with the patient's original planned dose.

The same dose reconstruction method was used to create the modeled dose plan without MLC tracking; however, the MLC positions from the patient's original treatment plan were used rather than the treatment MLC positions. The without-MLC tracking plan was imported into the treatment planning system and calculated for comparison with the original planned dose.

Statistical analysis

Dose-volume histograms for the clinical target volume (CTV), PTV, rectum, and bladder were computed from both the treated and without-MLC tracking dose distributions for each individual fraction, along with those of the patient's original planned dose distribution. The hypothesis that MLC tracking improves the consistency between the planned and treated with MLC tracking values over that without MLC tracking was tested for each dose-volume value via analysis of variance using the *F* test. The non- normality of the dose-volume points was confirmed using the Kolmogorov-Smirnov test.

Results

For the 15 patients in the study, 513 fractions were deliv- ered, all successfully with MLC tracking. One of the tracking patients was unable to be set up at the planning isocenter owing to body habitus and so was treated with an offset of approximately 3 mm with MLC tracking for 21 of the 40 fractions. These 21 fractions were not used for either the motion or dose reconstruction analysis. A further 17 fractions over the patient cohort were not used for motion or dose reconstruction analysis owing to machine faults, unrelated to MLC tracking, resulting in the data files created during the delivery not being compatible with the dose reconstruction software.

Intrafraction motion

Statistics of the prostate motion while the treatment beam was on for 475 fractions show that the average mean displacement for the fractions was 1.4 mm, with the highest mean 3-dimensional (3D) displacement for an individual fraction of 6.4 mm. The total percentage of treatment time that the displacement of the target was above 3, 5, 7, and 10 mm for all 475 fractions was 4%, 0.7%, 0.3%, and 0%, respectively. The maximum percentage of time the target moved further than 3, 5, 7, and 10 mm for individual fractions was 96%, 66%, 45%, and 4.7%, respectively. Although 3D displacements of >8 mm were observed, motion exceeding 8 mm in any of the 3 patient dimensions or those of the beams-eye view did not occur, and therefore no beam holds were asserted. The mean 3D displacement for 95% of the fractions was <2.5 mm, and only 8 of the 475 fractions had a mean displacement >3 mm, as can be seen in Figure 2.

Dose reconstruction comparison

Dose reconstruction was performed for 460 2-Gy fractions, 11 boost (10-Gy) fractions, and 4 3-Gy fractions.

For each individual fraction, 3 dose distributions were compared. Figure 3 compares these different dose distributions for a single (2-Gy) fraction, with a mean displacement and standard deviation of 3.6 ± 3.3 mm and a range of 0.5-9.2 mm. The reconstructed treated dose (with MLC tracking) (center) and the reconstructed without-MLC tracking dose (right) were both compared with the original planned dose (left). Using a dose-volume histogram (Fig. 4), the percentage difference from the planned value for dose-volume points PTV $D_{99\%}$, CTV $D_{99\%}$, rectum $V_{65\%}$, and bladder $V_{65\%}$ was calculated. For this individual fraction the difference from the planned PTV $D_{99\%}$, CTV $D_{99\%}$, rectum $V_{65\%}$, and bladder $V_{65\%}$ values were 0.05%, - 1.7%, 9.1%, and - 3.0%, respectively, for the treated dose and - 18.1%, - 7.9%, 41.3%, and - 33.4% for the without-MLC tracking dose distribution.

The mean difference and standard deviation for all 475 individual fractions for PTV $D_{99\%}$ of the treated (with MLC tracking) from the planned PTV $D_{99\%}$ was - 0.8% ±1.1% (Fig. 5a). Without MLC tracking, the mean difference and standard deviation from planned for the same dose-volume point was - 2.1% ± 2.7%. The CTV $D_{99\%}$ mean and standard deviation for the treated and the without-MLC tracking dose distributions were −0.6% ± 0.8% and −0.6% ± 1.1%, respectively. For the organs at risk, the dose-volume points of the rectum $V_{65\%}$ and bladder $V_{65\%}$ were assessed

(Fig. 5b), with the mean and standard deviation from planned of the treated dose being 1.6% ± 7.9% and 0.5% ± 4.4%, respectively, and for the without-MLC tracking doses, - 1.2% ± 18% and 0.0 ± 9.2%, respectively. The *P* value for all dose-volume points for 475 fractions was <.001.

The average mean displacement for the 9 treated 10-Gy fractions alone was 1.4 mm. The mean and standard deviation from planned for the PTV $D_{99\%}$ treated and without-MLC tracking doses were 0.2% ± 1.8% and - 0.9% ± 2.9%, respectively. The CTV $D_{99\%}$ mean and standard deviations from planned for the treated and without-MLC tracking doses were 0.2% ± 1.2% and 0.3% ± 0.8%, respectively. The rectum $V_{65\%}$ and bladder $V_{65\%}$ mean and standard deviation of the treated dose from planned were -19.4% ± 20% and 9.4% ± 16%. For the without-MLC tracking dose, the values were -21.2% ± 45% and 12.6% ± 37%. All 4 sets of data for the PTV and CTV were found to be normally distributed, whereas the rectum and bladder data were not. The difference invariance from planned for the PTV and CTV data was not significant, with *P*=.08 and *P*=.12. The normal tissues were found to have a significant dif ference in variance from planned for treated versus without-MLC tracking, with *P*=.01 and *P*=.006, respectively.

Discussion

Multileaf collimator tracking has been implemented for the first time in a prospective prostate cancer clinical trial. The results of this study show that the treated doses of MLC tracking treatments vary less from the planned dose than the equivalent treatment deliveries modeled without MLC tracking for prostate cancer radiation therapy.

This study shows that MLC tracking can reduce the variance from the planned dose to that which is delivered to the patient. These prospective results are consistent with a retrospective preclinical MLC tracking dose reconstruction study (11). A simulation study performed using dose reconstruction for conventional and subvolume boost treatments for prostate showed that MLC tracking is effective at mitigating the dosimetric effects of prostate motion and allows for successful GTV and PTV dose delivery (14), as demonstrated in the present study. The dosimetric results for the without-MLC tracking delivery also corresponds closely with other observational prostate dose reconstruction studies (15, 16) that have modeled the effect of intrafraction prostate motion on the dose delivery of standard non-MLC tracking treatments. The outlier fractions for which the dose distribution was improved by MLC tracking tended to be lower PTV and CTV doses, lower rectum doses, and higher bladder doses. The normal tissue variations are likely due to the drift of the prostate for some fractions in the posterioreinferior direction due to bladder filling: the posterior wall of the bladder shifts into a higher dose region, whereas the rectum is shifted away (17). The large range of results for the rectum and bladder appear because the percentage change is assessed in relation to the planned percentage of the organ volume receiving 65% of the prescription dose and not the entire organ.

The dosimetric results show that tracking had little effect on the mean difference from the planned doses; it did, however, reduce the effect of outlier fractions with large underdoses of the targets. This increased certainty in de- livery accuracy will allow for the possibility of reducing margins for prostate treatments and enable more consistent delivery of SBRT prostate treatments.

The prostate motions measured during treatment for this study are similar to other

observational study results (17, 18), with a similar percentage of fractions with high mean displacements of >3 mm. The data from this study do show a greater percentage of fractions with a mean displacement in the 1- to 3-mm range and fewer in the 0- to 1-mm range. This is likely due to several factors: previous studies did not correct for patient motion after the initial setup or imaging; 1 study assessed all motion relative to the initial setup image position rather than the planned position (18); and throughout the present study couch corrections were made and the patient position shifted when the prostate moved >2.5 mm (as observed by Calypso) in any of the 3 dimensions before the first arc and between treatment arcs. This means that the prostate motion of this study has a slightly different displacement distribution but is still comparable to other prostate motion data.

Because of the pre- and inter-arc couch corrections during some fraction deliveries, the dose distributions of these modeled fractions, without MLC tracking, likely underestimate the dosimetric variability present for regular standard of care, in which correction is made to patient position after initial imaging. These fractions are more consistent with the scenario in which an inter-arc patient position correction is performed.

A limitation of this first implementation of MLC tracking is that it only corrects for translation of the target volume and does not account for either rotation or deformation. This limitation is mirrored in the dose reconstruction process (12) and will likely be mitigated in the future with further development of the MLC tracking technology to account for rotation and deformation (19, 20). This increase in information obtained during treatment would also help to inform dose reconstruction for better estimates of delivered treated doses. This issue also leads to another limitation of the dose reconstruction process that models the organs at risk (eg rectum and bladder) motion with the same trajectory as the target volume, with no deformation or volume changes accounted for.

Conclusions

Multileaf collimator tracking has been implemented clinically for the first time in a prostate cancer VMAT trial. The application of MLC tracking was shown to improve the consistency between the planned and delivered doses compared with doses that would have been delivered without MLC tracking. The implications of this finding are potentially improved patient outcomes, reduced margins for future studies, and more reliable dose-volume data for radiobiological parameter determination. Multileaf collimator tracking is translatable to other tumor types as an effective motion management strategy. Future research will develop and translate to clinical practice solutions to tumor rotation and deformation, including differential motion of multiple targets.

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Table 1. Patient Cohort

Table 1. Patient cohort

Characteristic	Value
Age (y)	69 (57-81)
PSA (ng/mL)	10.9 (1.1-33)
Gleason score	9 (7-10)
Clinical staging	
$T_{1C}N_0M_0$	4
$T_{2A}N_0M_0$	3
$T_{2B}N_0M_0$	3
$T_{2C}N_0M_0$	1
$T_2N_1M_0$	1
$T_{3A}N_0M_0$	1
$T_{3B}N_0M_0$	2
Fractionation schedules	
80 Gy/40 Fx	9
20 Gy/2 Fx + 46 Gy/23 Fx	4
Altered fractionation*	2
PTV volume (cm^3)	132 (62-185)

Abbreviations: Fx = treatment fraction; PSA = prostate-specific antigen; PTV = planning target volume.

Values are number or median (range).

*

10 Gy/1 Fx + 60 Gy/30 Fx; 20 Gy/2 Fx + 32 Gy/16 Fx + 12 Gy/4 Fx.

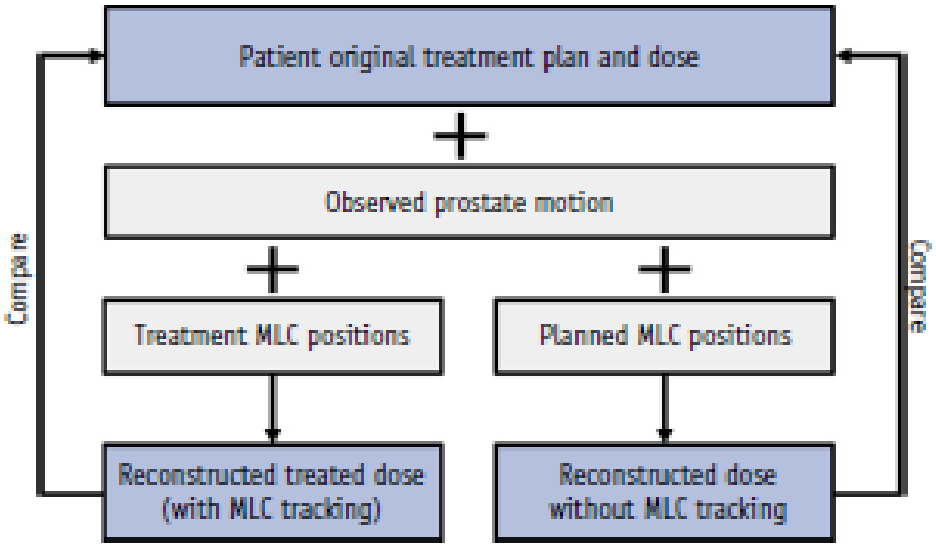

Figure 1. Dose comparison process for individual fractions; separate treated doses (with multileaf collimator [MLC] tracking) and without-MLC tracking doses are created using dose reconstruction and compared with the original planned dose. The treated dose is created by combining the original treatment plan with the observed prostate motion during treatment and the treatment MLC positions, whereas the without-MLC tracking dose is created by combining the original treatment plan and observed prostate motion alone.

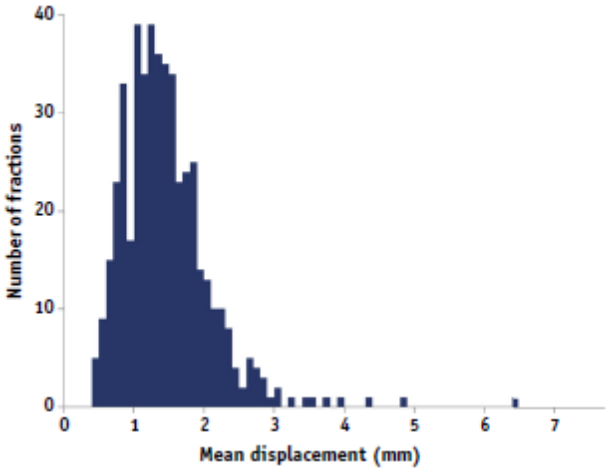

Figure 2. Frequency histogram of the mean displacement for 475 multileaf collimator tracking treatment fractions

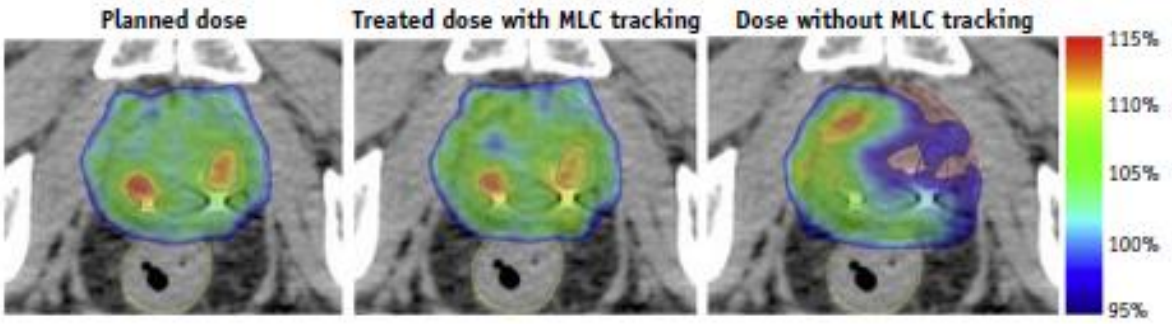

Figure 3. The 3 dose distributions (≥95% isodose) for a single 2-Gy fraction with a mean displacement of 3.6 mm with the planning target volume (red) and contoured gross tumor volume (blue). The planned dose distribution (left), the treated with MLC tracking dose (center), and the modeled without multileaf collimator (MLC) tracking dose (right).

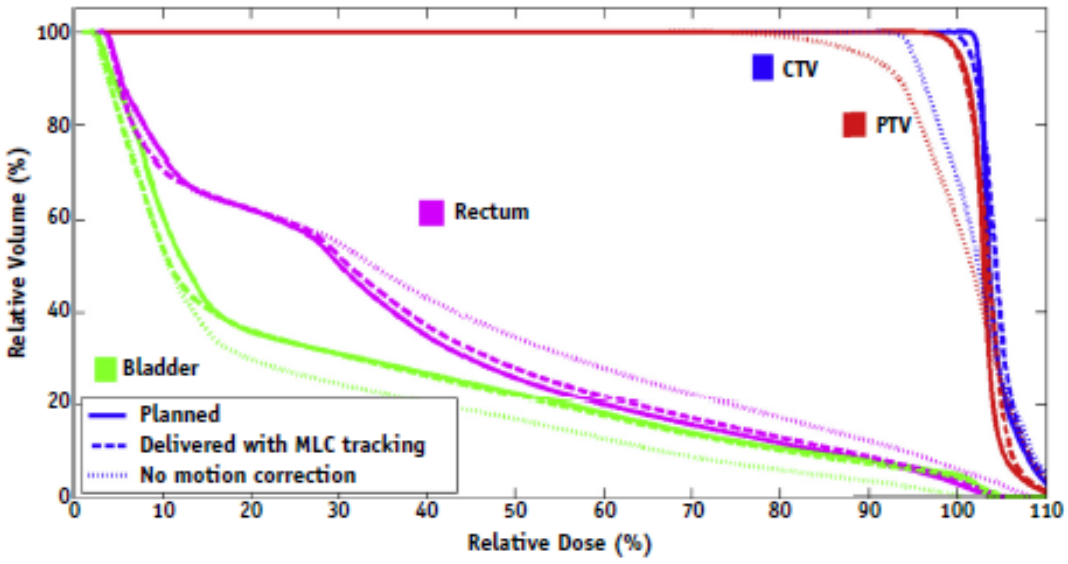

Figure 4. Comparison of dose-volume histograms for the dose distributions in Fig. 3 of a 2-Gy fraction with a mean displacement of 3.6 mm. The planned dose (solid line), the treated with MLC tracking dose (dashed line), and the modeled without MLC tracking dose (dotted line). CTV = clinical target volume; PTV = planning target volume.

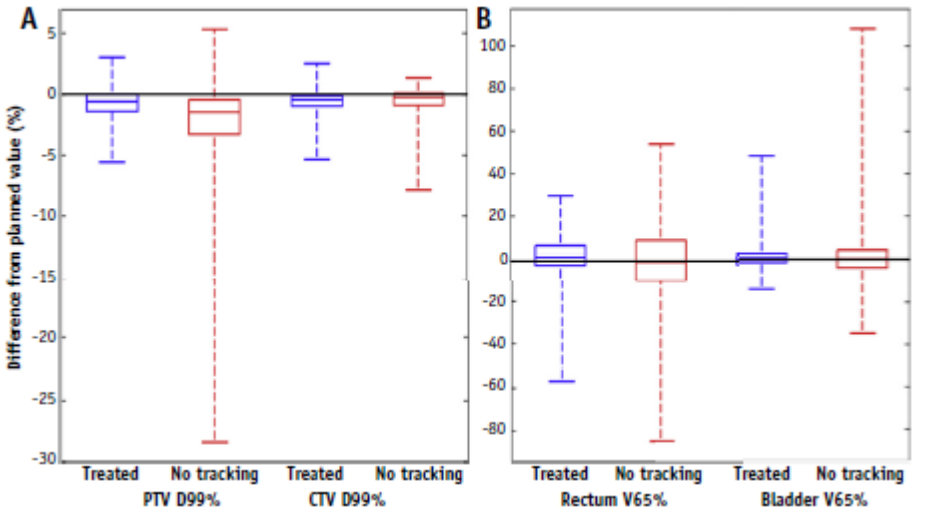

Fig. 5. The calculated percentage dose difference (n=475) from the planned value for the treated (blue) and without multileaf collimator tracking (red) dose distributions for (a) planning target volume (PTV) and clinical target volume (CTV) $D_{99\%}$ values, and (b) rectum and bladder $V_{65\%}$ values. Represented by median and 25th and 75th percentile. Vertical lines indicate the maximum and minimum values.