The First Clinical Implementation of Real-time Image-Guided Adaptive Radiotherapy using a Standard Linear Accelerator

P. Keall[1], D. T. Nguyen[1], R. O'Brien[1], V. Caillet[1,2], E. Hewson,[1] P. R. Poulsen[3], R. Bromley[2], L. Bell[2], T. Eade[2,1], A. Kneebone[2,1], J. Martin[4] and J.T. Booth[2,1]

[1]*University of Sydney, Sydney, Australia,* [2]*Royal North Shore Hospital, Sydney, Australia,* [3]*Aarhus University Hospital, Aarhus, Denmark,* [4]*Calvary Mater Newcastle Hospital, Newcastle, Australia*

Key words: Kilovoltage intrafraction monitoring (KIM), multileaf collimator tracking, real-time image-guided adaptive radiotherapy, geometric accuracy, dose reconstruction

ABSTRACT

Purpose: Until now, real-time image guided adaptive radiation therapy (IGART) has been the domain of dedicated cancer radiotherapy systems. The purpose of this study was to clinically implement and investigate real-time IGART using a standard linear accelerator.

Materials/Methods: We developed and implemented two real-time technologies for standard linear accelerators: (1) Kilovoltage Intrafraction Monitoring (KIM) that finds the target and (2) multileaf collimator (MLC) tracking that aligns the radiation beam to the target. Eight prostate SABR patients were treated with this real-time IGART technology. The feasibility, geometric accuracy and the dosimetric fidelity were measured.

Results: Thirty-nine out of forty fractions with real-time IGART were successful (95% confidence interval 87%-100%). The geometric accuracy of the KIM system was -0.1±0.4, 0.2±0.2 and -0.1±0.6 mm in the LR, SI and AP directions, respectively. The dose reconstruction showed that real-time IGART more closely reproduced the planned dose than that without IGART. For the largest motion fraction, with real-time IGART 100% of the CTV received the prescribed dose; without real-time IGART only 95% of the CTV would have received the prescribed dose.

Conclusion: The clinical implementation of real-time image-guided adaptive radiotherapy on a standard linear accelerator using KIM and MLC tracking is feasible. This achievement paves the way for real-time IGART to be a mainstream treatment option.

INTRODUCTION

Until now, real-time image-guided adaptive radiation therapy (IGART) has been the domain of dedicated and often expensive cancer radiotherapy systems such as the CyberKnife Synchrony[1] and Mitsubishi/BrainLab Vero.[2] The purpose of this study was to clinically implement and investigate real-time IGART using a standard linear accelerator.

We developed two real-time image guidance technologies for standard linear accelerators: (1) Kilovoltage Intrafraction Monitoring (KIM) that finds the target position in real-time during radiotherapy and (2) multileaf collimator (MLC) tracking that aligns the radiation beam to the moving target.

KIM is an image-based real-time localization method first clinically implemented in 2014[3] that has been used in over 1200 treatment fractions for prostate cancer in five different cancer centers. Prior to the current study, all treatments with KIM have been gated. When the observed target motion exceeded a threshold the treatment was interrupted and a manual couch shift was performed to realign the target with the radiation beam. The motion threshold is typically ≥3 mm displacement for 5 seconds for conventional fractionation, and ≥2mm of motion for 5 seconds for stereotactic ablative body radiotherapy (SABR).

MLC tracking is a real-time adaptive radiotherapy method first clinically implemented in 2013[4] that has been used in over 800 treatment fractions for prostate and lung cancer. Prior to the current study, the clinical implementation of MLC tracking had been restricted to a research version of the Calypso[5] electromagnetic transponder-guided localization method. Calypso is an add-on to the standard equipped linear accelerator, and requires additional hardware. KIM is a software-based real-time system that uses the hardware of a standard equipped linear accelerator.

When put together, KIM and MLC tracking enable real-time IGART using a standard linear accelerator without any additional hardware. The purpose of this study was to clinically implement and investigate real-time IGART using KIM and MLC tracking.

METHODS

Clinical details

Eight prostate SABR patients enrolled on the TROG 15.01 SPARK (NCT02397317) clinical trial were treated. SPARK = **S**tereotactic **P**rostate **A**daptive **R**adiotherapy Utilising **K**ilovoltage Intrafraction Monitoring. The CTV margins were 5 mm isotropically except 3 mm posteriorly. The prescribed dose was 36.25 Gy to 95% of the PTV in five 7.25 Gy fractions. Study protocol details are given in reference 6 and https://clinicaltrials.gov/ct2/show/NCT02397317.

Clinical process

Patients were implanted with three gold fiducials markers and hydrogel one week prior to simulation. Simulation images were acquired on a Philips BigBore CT scanner with 1.5mm slices. Fiducial markers were defined as high definition structures and the centroid position of the three fiducials was defined to be the treatment isocenter. Eligibility criteria included a patient lateral dimension of <40cm at level of isocenter and correct positioning of fiducials (three markers intact and no markers at the same superior-inferior level). A dual arc volumetric modulated arc treatment was planned using Eclipse v13.6 (Varian Medical Systems, Palo Alto) to satisfy the SPARK trial dose-volume constraints. After the treatment plan optimization was complete, the field size was manually enlarged by 1.6cm (0.8cm on each side) without changing the MLC to allow MLC tracking without causing a beam hold if the target moves below the jaw. The change in jaw position required the dose to be recalculated and the plan was renormalized, and the dose-volume constraints were reconfirmed against SPARK trial requirements.

Patients were treated on a Varian Trilogy linac with Millennium MLC. Positioning was verified with CBCT to align fiducials and cross-checked with CTV and PTV structure overlay. Framegrabber hardware cables and acquisition software (Varian iTools) were used to acquire kV and MV images

during treatment. The images were streamed to a research computer on which the KIM and MLC tracking programs were installed. The research computer was integrated into the linac intranet to enable MLC positions and beam holds to be sent from the MLC tracking software to the linac. The KIM software was activated following patient alignment and preceding treatment delivery, requiring the patient's implanted marker positions determined from the treatment plan to be loaded and acquisition of kV fluoroscopy during a 120° imaging only arc to populate the KIM probability density function.[3] The MLC tracking software was activated with the MLC positions as a function of gantry angle and monitor unit obtained by reading the DICOM RT plan. Treatment was delivered with kV fluoroscopy (125kVp, 80mA, 13 ms, 6×6cm^2, 10Hz). The estimated additional kV dose from the KIM procedure is 0.4Gy.[7] A gating threshold of 1cm was applied. Following treatment a second CBCT was acquired according to the SPARK protocol.

Quality assurance
For the TROG 15.01 SPARK trial, in addition to routine departmental procedures, the contours and dose distributions for each patient's plan were independently reviewed. The KIM and MLC tracking quality assurance processes were based on previous publications.[8,9] System tests (repeated monthly) included coordinate system check, dynamic tracking accuracy, treatment interruption, latency measurement, dosimetric accuracy for standard delivery and kV panel offset correction with gantry angle. We also deployed software-based, patient-specific geometric and patient-specific dosimetric controls as a comprehensive quality assurance program applied pre-treatment, during treatment and post-treatment. The pre-treatment quality assurance included:
- Planning task checklist.
- Monitor Unit check with IMSURE (Standard Imaging) with a tolerance of ±3%.
- Delivery of the plan using KIM and MLC tracking to a motion phantom programmed with typical prostate motions to determine deliverability (i.e. no beam holds) and geometric accuracy (tolerance as mean value and root mean square error <1mm)
- Measurement of delivered dose with MLC tracking applied to a programmable motion phantom holding an anthropomorphic phantom containing GAF film in the coronal plane attached to HexaMotion (ScandiDos, Uppsala, Sweden). Applied tolerance of 98% of points within 2%/2mm gamma comparing measurement with motion and tracking against measurement without motion. A further comparison was made between measured and planned dose distribution.

The during-treatment quality assurance included:
- Visual inspection of segmentation and that the reported motion corresponded to segmented positions relative to planned positions
- Software controlled measures (inside KIM software) leading to beam hold interlocks on the linear accelerator, including: loss of communication between KIM, MLC tracking or MLC controller; detection of motion outside tracking zone; reduction of correlation below a threshold (to detect migration, or segmentation error); change in inter-marker distances (to detect deformation, segmentation error, or 2D→3D conversion error); acceleration of centroid over a threshold value (to detect 2D→3D conversion error)

The post-treatment quality assurance included:
- kV/MV triangulation as ground truth and comparison with KIM real-time trajectory to assure accuracy of prostate motion trajectory feeding MLC tracking
- reconstruction of delivered dose utilizing prostate motion trajectory, MLC logfiles and original treatment plan as described elsewhere[10,11]

Measurements
Three factors affecting the patient's treatment were analyzed: feasibility, geometric accuracy of the KIM system, and dosimetric fidelity of the integrated KIM-MLC real-time IGART system.
1. *Feasibility* was measured using maximum likelihood estimates (Matlab's binofit function) assuming a binomial distribution of a successful or unsuccessful treatment. A successful

treatment was defined as the entire treatment fraction was delivered with KIM-guided MLC tracking.

2. The *geometric accuracy of the KIM system* was measured by comparing the KIM-measured motion to the motion measured using post-treatment kV/MV triangulation.

3. The *dosimetric fidelity of the integrated KIM-MLC IGART system* was measured using a previously published dose reconstruction technique.[10] The dose reconstruction method combines the original treatment plan, the KIM-measured motion files and the treatment log files that have the MLC leaf positions, gantry angles, couch shifts and monitor units delivered, to estimate the dose delivered in the presence of motion, both with and without IGART. A limitation of the dose reconstruction method is that the dose reconstruction is performed on the initial planning CT scan to avoid the uncertainties introduced by both dose calculation on CBCT scans and deformably registering CBCT to CT.

The study design is shown schematically in Figure 1.
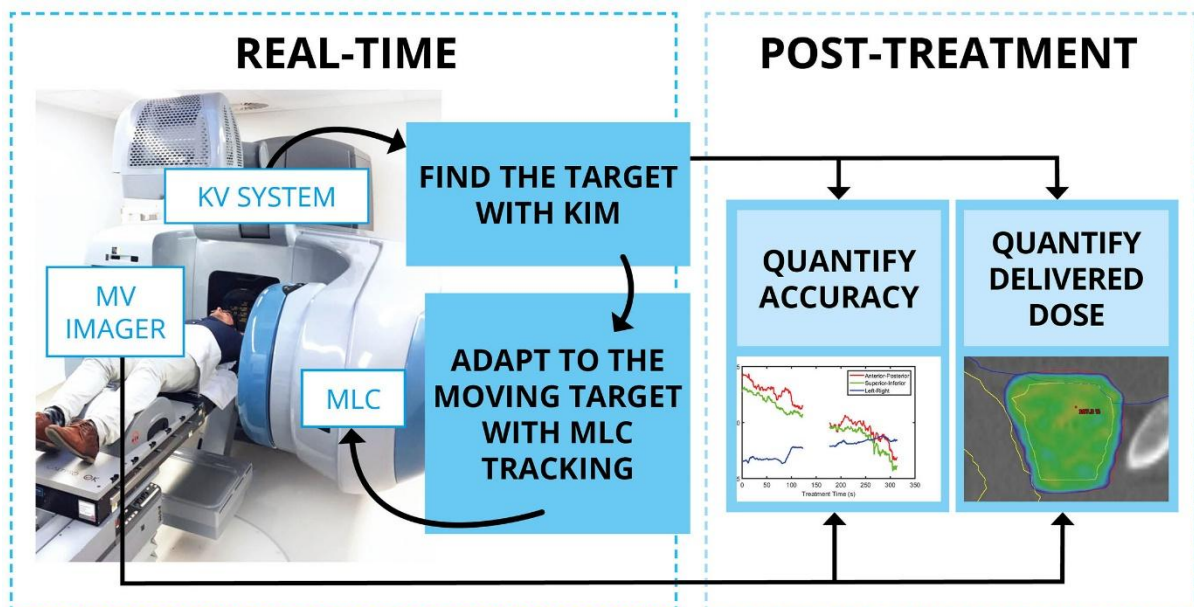
Figure 1. A schematic of the integration of real-time IGART on a standard linac. The two experimental technologies to find the target and hit the target, respectively KIM and MLC tracking, are integrated to enable real-time IGART.

RESULTS

Feasibility

Thirty-nine out of forty treatment fractions with real-time IGART using the KIM and MLC tracking technologies were successful. This yields a maximum likelihood probability estimate for feasibility of 97.5%, with 95% confidence intervals of (87%, 100%). One of the 40 fractions (patient 2 fraction 1) only used KIM with gating and not MLC tracking. For patient safety reasons, MLC tracking was not attempted in this fraction as quality assurance processes had not been completed following a software revision. A video of the KIM and MLC tracking software interfaces at the treatment console is shown in supplementary material video.

The time for the real-time IGART SABR treatment fractions from the end of the cone beam alignment to the completion of treatment delivery ranged from 5.6 to 15 minutes, with a mean of 7.7 and a median of 7.0 minutes.

Geometric accuracy of the KIM system

Overall, prostate motion greater than 3, 5 and 7 mm was observed in 38%, 9.0% and 6.2% of the 40 treatment fractions respectively. The mean±standard deviation of the geometric accuracy of the KIM

system over all 40 fractions was -0.1±0.4, 0.2±0.2 and -0.1±0.6 mm in the LR, SI and AP directions, respectively.

*Dosimetric fidelity of the integrated KIM-MLC IGART system*
The dose reconstruction results showed that real-time IGART reproduced the planned dose in the presence of intrafraction motion. The CTV and PTV doses were consistently higher with IGART than without IGART. The rectal and bladder doses were consistently closer to that planned for each fraction with IGART than without IGART. Dose volume histograms of the doses summed over each fraction are shown in Figure 2.
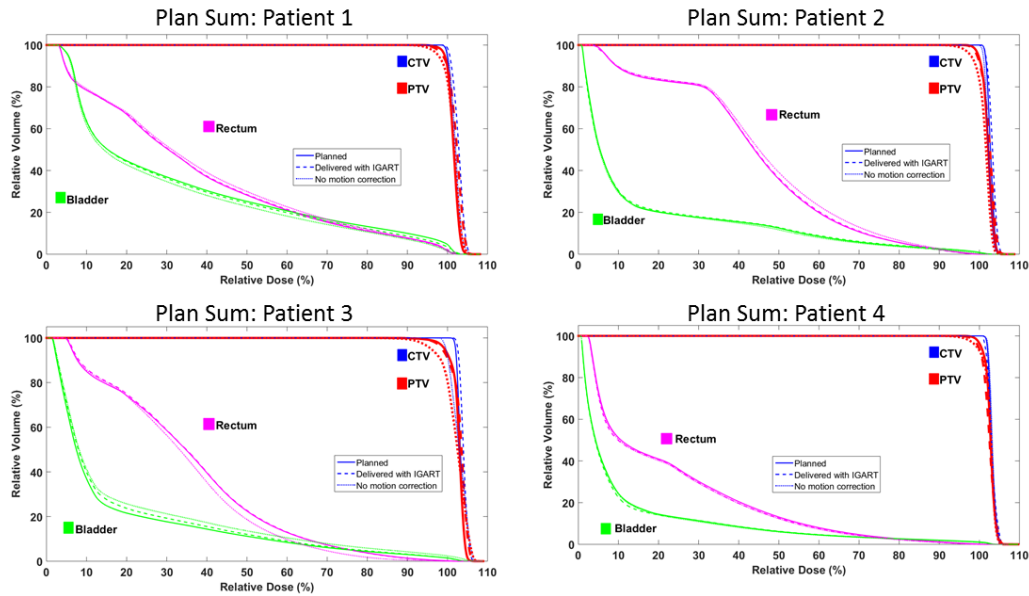
Figure 2. Dose volume histograms (DVHs) for planned, delivered with real-time IGART, and estimated without real-time IGART (no motion correction) for the first four SABR patients treated with KIM and MLC tracking. The plan sum DVHs represent the dose summed over each of the five fractions.

Individual fraction analysis
For prostate cancer SABR, there can often be little target motion. The cases of most interest from a real-time tracking perspective are those at the tails of the distribution where motion management is more critical. We focused the individual analysis on the fraction (patient 3, fraction 5) with the largest observed target motion (most time spent ≥3 mm from isocenter). For this fraction, where over 8 mm of target motion was observed from the start to the end of treatment, the target motion, isodose distributions and dose volume histograms are shown in Figure 3, Figure 4 and Figure 5 respectively. The 5 mm displacement at the start of treatment occurred due to prostate motion that occurred after the cone beam CT acquisition and before the start of treatment.
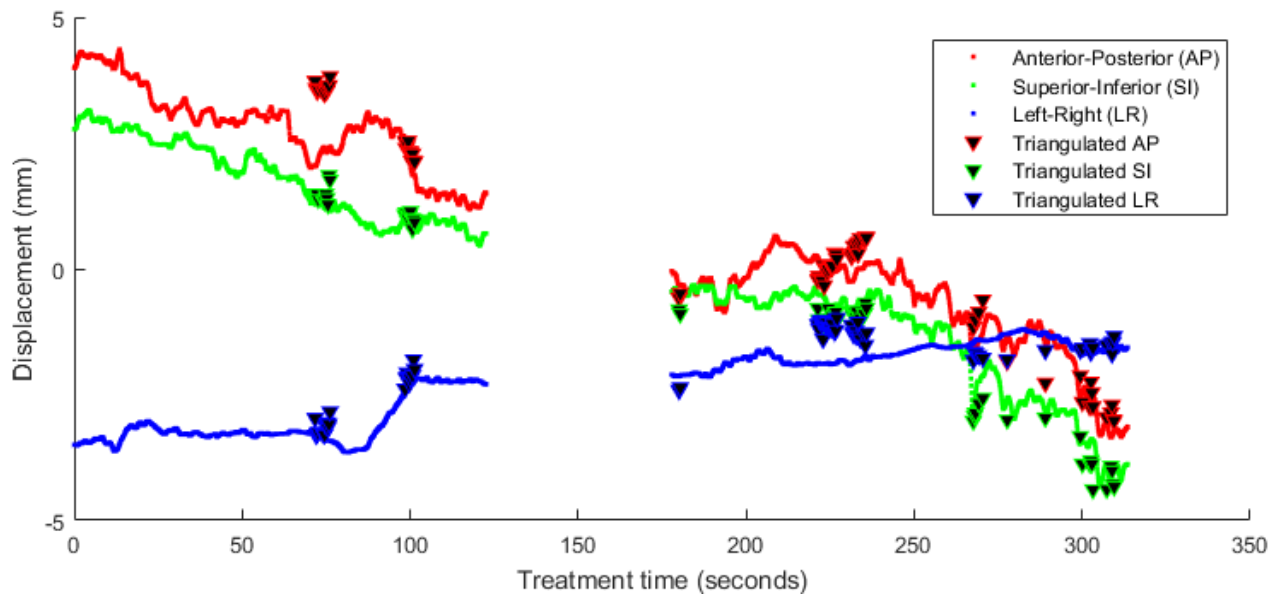
Figure 3. The KIM-measured target motion for the treatment fraction with the largest measured motion (patient 3 fraction 5) for the dual arc SBRT VMAT treatment. The gap in data is the time between the two treatment arcs to allow for collimator rotation. The kV beam was turned off to reduce imaging dose. Overlaid are the post-treatment measured kV/MV triangulated positions.
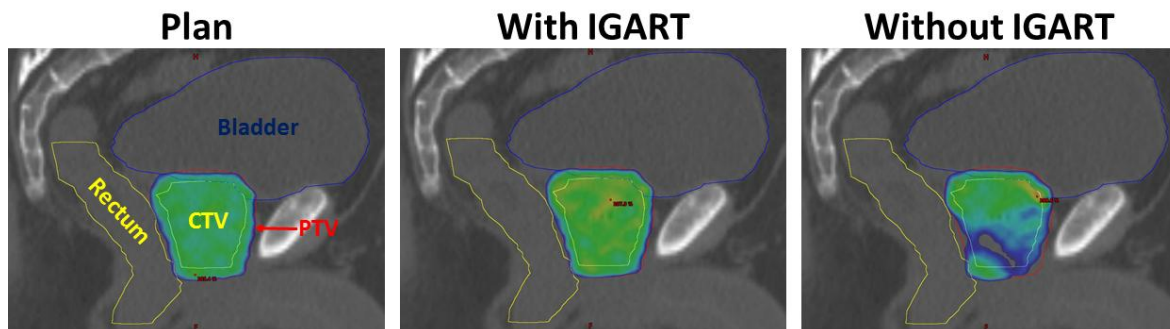
Figure 4. Isodose distributions for planned (left), delivered with real-time IGART (middle), and estimated without real-time IGART (right) for the fraction with the motion shown in Figure 3. The isodose range is from the PTV 95% (prescribed dose) to 110%.
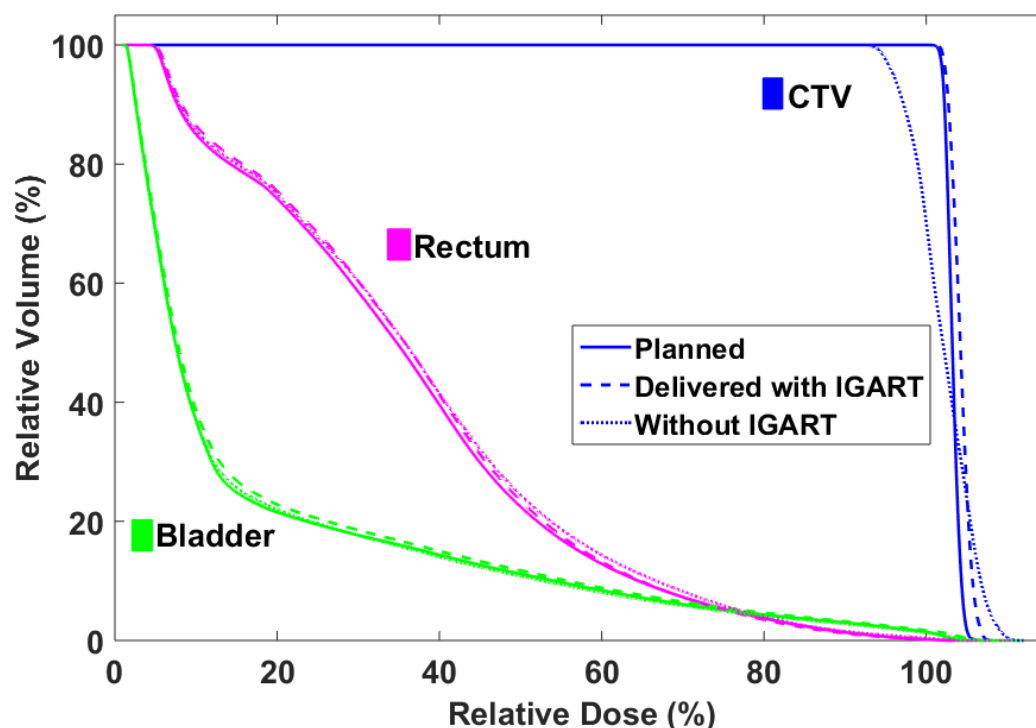
Figure 5. Dose-volume histograms of the planned (continuous line), delivered with real-time IGART (dashed line), and estimated without real-time IGART (dotted line) for the fraction shown in Figure 3 and Figure 4.

For the largest motion fraction (Figure 3), the mean±one standard deviation of the geometric accuracy of the KIM system was -0.3±0.6, 0.4±0.2 and -0.1±0.6 mm in the LR, SI and AP directions, respectively, indicating that the geometric accuracy was not affected by the motion magnitude. Without KIM, the geometric accuracy of this treatment would have been -2.3±0.8, 0.1±1.9 and 0.9±2.0 mm in the LR, SI and AP directions respectively. Analyzing the dose volume histogram for the largest motion fraction (Figure 5), with real-time IGART 100% of the CTV received the prescribed dose; without real-time IGART only 95% of the CTV would have received the prescribed dose.

DISCUSSION

It is acknowledged that motion management is more important for SABR treatments given the fewer number of fractions.[12] In this study, a standard linear accelerator was used to enable real-time IGART for eight prostate cancer SABR patients by utilizing two emerging technologies, KIM and MLC tracking. To put this achievement in context using Australia as an example, over 95% of the cancer radiotherapy systems are standard C-arm linacs. KIM and MLC tracking are software tools that enable these standard linacs to be used as real-time image-guided adaptive radiotherapy systems. Therefore, there is potential for these technologies to be broadly implemented for real-time adaptive radiotherapy.

Intratreatment 2D guidance on Elekta and Varian systems has been implemented using the in-house SeedTracker system[13] and the vendor-supplied Triggered Imaging package.[14] These 2D imaging approaches have been clinically implemented for gating and have resulted in CTV-PTV margin reduction.[14] However the 2D information lacks the motion component perpendicular to the treatment beam in one direction and limits the ability to perform more advanced functions that are enabled by 3D motion monitoring, such as MLC tracking, couch tracking or dose reconstruction. Common to all of these methods is the additional kV imaging dose that should be kept to a minimum whilst maintaining the utility of real-time guidance.

For the task of real-time guidance, in addition to KIM, other marker-based kilovoltage imaging approaches to obtain the 3D target position from gantry-mounted 2D images have been published, e.g. the the arbitrary-shape PDF method.[15] KIM is the only approach in this class that has been clinically implemented. However, different formalisms to solve the 2D→3D problem would presumably offer similar performance.

Only adaptation to 3D translational motion was implemented in this study. KIM measures the translation and rotation (6 degree-of-freedom motion) of the target,[16] and MLC tracking has been experimentally demonstrated to correct for in-plane rotation[17] and potentially can correct for out-of-plane rotation if dose accumulation and optimization is performed in the patient anatomy. Explicitly adapting for rotation is part of future KIM-MLC tracking integration research.

For prostate cancer radiotherapy, gating and MLC tracking are probably equivalent in accuracy and the dosimetric implcations.[18] MLC tracking is slightly more efficient as it enables treatment to start immediately after correction and obviates the need for corrections during treatment. In the SPARK trial, for the KIM-guided gating treatments (non-MLC tracking), there is on average one intra-treatment gating event per fraction using a threshold of motion of the target moving more than 2mm from isocenter for more than 5 seconds. MLC tracking has a smoother workflow, higher degree of automation and less operator involvement than gating. Although large motion is relatively rare for prostate SABR, real-time IGART provides a safety net that ensures accurate dose delivery even when the large motion occurs. Real-time IGART will likely be more beneficial for future-planned applications of KIM-MLC tracking to thoracic and abdominal sites where motion can be large and variable, enabling accurate and efficient treatment delivery.

A similar goal of real-time IGART on a standard linear accelerator couch could be achieved by implementing KIM with couch tracking.[19-21] Couch tracking is attractive for prostate motion correction as the motion is generally slow and small, and also very intuitive – the KIM motion signal should be close to (0,0,0) at all times as the couch would shift the patient (and target) in the opposite direction to the KIM-measured motion. From a future perspective of integrating KIM with couch tracking for rotation, the couch is limited to correcting only small angles in the roll and pitch directions, and yaw corrections may also introduce a collision risk. Rotational correction with the couch will alter the beam path through the patient. Couch tracking will also be limited for advanced treatments where deformation correction may be needed, for example when treating locally advanced prostate cancer and the prostate moves with respect to the nodes,[22-24] requiring the beam shape to change.

CONCLUSION

The clinical implementation of real-time IGART using a standard linear accelerator using KIM and MLC tracking is feasible. This achievement paves the way for this technology to be tested more broadly, enabling more accurate radiotherapy on widely available linear accelerators, and ushering in the era of real-time radiotherapy as a mainstream treatment option.

REFERENCES

1. Kilby W, Dooley J, Kuduvalli G, Sayeh S, Maurer Jr C. The CyberKnife® robotic radiosurgery system in 2010. *Technology in cancer research & treatment.* 2010;9(5):433-452.
2. Kamino Y, Takayama K, Kokubo M, et al. Development of a four-dimensional image-guided radiotherapy system with a gimbaled X-ray head. *International Journal of Radiation Oncology* Biology* Physics.* 2006;66(1):271-278.
3. Keall PJ, Ng JA, O'Brien R, et al. The first clinical treatment with kilovoltage intrafraction monitoring (KIM): A real-time image guidance method. *Med Phys.* 2015;42(1):354-358.
4. Keall PJ, Colvill E, O'Brien R, et al. The first clinical implementation of electromagnetic transponder-guided MLC tracking. *Med Phys.* 2014;41(2):1-5.
5. Kupelian P, Willoughby T, Mahadevan A, et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. *Int J Rad Onc Biol Phys.* 2007;67(4):1088-1098.
6. Keall P, Nguyen DT, O'Brien R, et al. Stereotactic Prostate Adaptive Radiotherapy utilising Kilovoltage Intrafraction Monitoring: the TROG 15.01 SPARK trial. *BMC Cancer.* 2017;17(1):180.
7. Legge K, Greer PB, Keall PJ, et al. TROG 15.01 SPARK trial multi-institutional imaging dose measurement. *Journal of applied clinical medical physics.* 2017;18(5):358-363.
8. Ng J, Booth J, O'Brien R, et al. Quality assurance for the clinical implementation of kilovoltage intrafraction monitoring for prostate cancer VMAT. *Med Phys.* 2014;41(11):111712.
9. Sawant A, Dieterich S, Svatos M, Keall P. Failure mode and effect analysis-based quality assurance for dynamic MLC tracking systems [published online ahead of print 2011/02/10]. *Med Phys.* 2010;37(12):6466-6479.
10. Poulsen PR, Schmidt ML, Keall P, Worm ES, Fledelius W, Hoffmann L. A method of dose reconstruction for moving targets compatible with dynamic treatments [published online ahead of print 2012/10/09]. *Med Phys.* 2012;39(10):6237-6246.
11. Colvill E, Booth JT, O'Brien R, et al. MLC Tracking Improves Dose Delivery for Prostate Cancer Radiotherapy: Results of the First Clinical Trial. *Int J Rad Onc Biol Phys.* 2015;92(5):1141-1147.
12. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. *Med Phys.* 2010;37(8):4078-4101.
13. Arumugam S, Sidhom M, Xing A, Holloway L. An online x-ray based position validation system for prostate hypofractionated radiotherapy. *Medical physics.* 2016;43(2):961-974.
14. Van der Weide L, Admiraal M, Rosario T. PO-0889: Intra-fraction re-setup with Triggered Imaging allows for margin reduction in prostate treatments. *Radiotherapy and Oncology.* 2016. (119):S427.
15. Li R, Fahimian BP, Xing L. A Bayesian approach to real-time 3D tumor localization via monoscopic x-ray imaging during treatment delivery. *Medical physics.* 2011;38(7):4205-4214.
16. Nguyen DT, O'Brien R, Kim J-H, et al. The first clinical implementation of a real-time six degree of freedom target tracking system during radiation therapy based on Kilovoltage Intrafraction Monitoring (KIM). *Radiotherapy and Oncology.* 2017;123(1):37-42.
17. Wu J, Ruan D, Cho B, et al. Electromagnetic detection and real-time DMLC adaptation to target rotation during radiotherapy [published online ahead of print 2011/10/22]. *Int J Radiat Oncol Biol Phys.* 2012;82(3):e545-553.
18. Colvill E, Poulsen PR, Booth J, O'Brien R, Ng J, Keall P. DMLC tracking and gating can improve dose coverage for prostate VMAT. *Med Phys.* 2014;41(9):091705.
19. D'Souza WD, Naqvi SA, Yu C, X. . Real-time intra-fraction-motion tracking using the treatment couch: a feasibility study. *Phys Med Biol.* 2005;50(17):4021.
20. Menten MJ, Guckenberger M, Herrmann C, et al. Comparison of a multileaf collimator tracking system and a robotic treatment couch tracking system for organ motion compensation during radiotherapy. *Medical physics.* 2012;39(11):7032-7041.

21.   Ehrbar S, Schmid S, Jöhl A, et al. Validation of dynamic treatment-couch tracking for prostate SBRT. *Medical Physics.* 2017;44(6):2466-2477.

22.   Ludlum E, Mu G, Weinberg V, Roach M, Verhey LJ, Xia P. An algorithm for shifting MLC shapes to adjust for daily prostate movement during concurrent treatment with pelvic lymph nodes. *Med Phys.* 2007;34(12):4750-4756.

23.   Kishan AU, Lamb JM, Jani SS, Kang JJ, Steinberg ML, King CR. Pelvic nodal dosing with registration to the prostate: Implications for high-risk prostate cancer patients receiving stereotactic body radiation therapy. *International Journal of Radiation Oncology* Biology* Physics.* 2015;91(4):832-839.

24.   Hsu A, Pawlicki T, Luxton G, Hara W, King CR. A study of image-guided intensity-modulated radiotherapy with fiducials for localized prostate cancer including pelvic lymph nodes. *International Journal of Radiation Oncology* Biology* Physics.* 2007;68(3):898-902.

Figure 1
Click here to download high resolution image

Plan Sum: Patient 1

Plan Sum: Patient 2

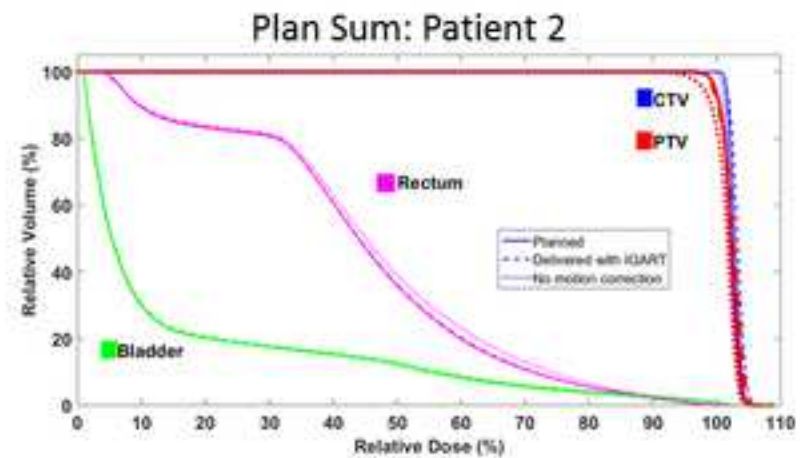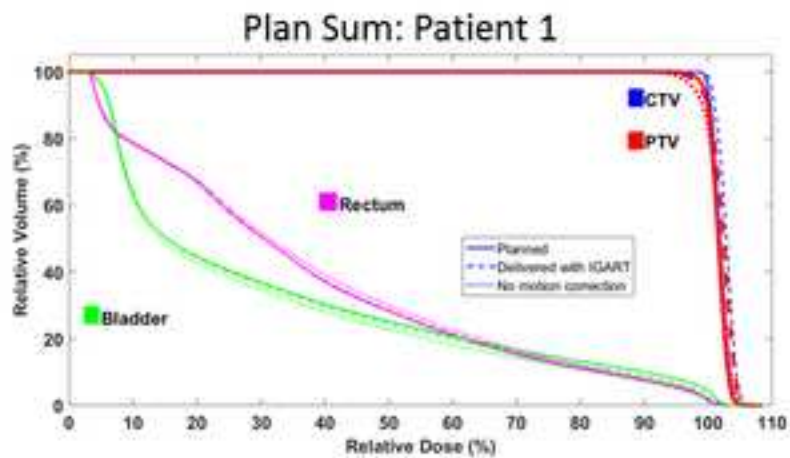Plan Sum: Patient 3

Plan Sum: Patient 4
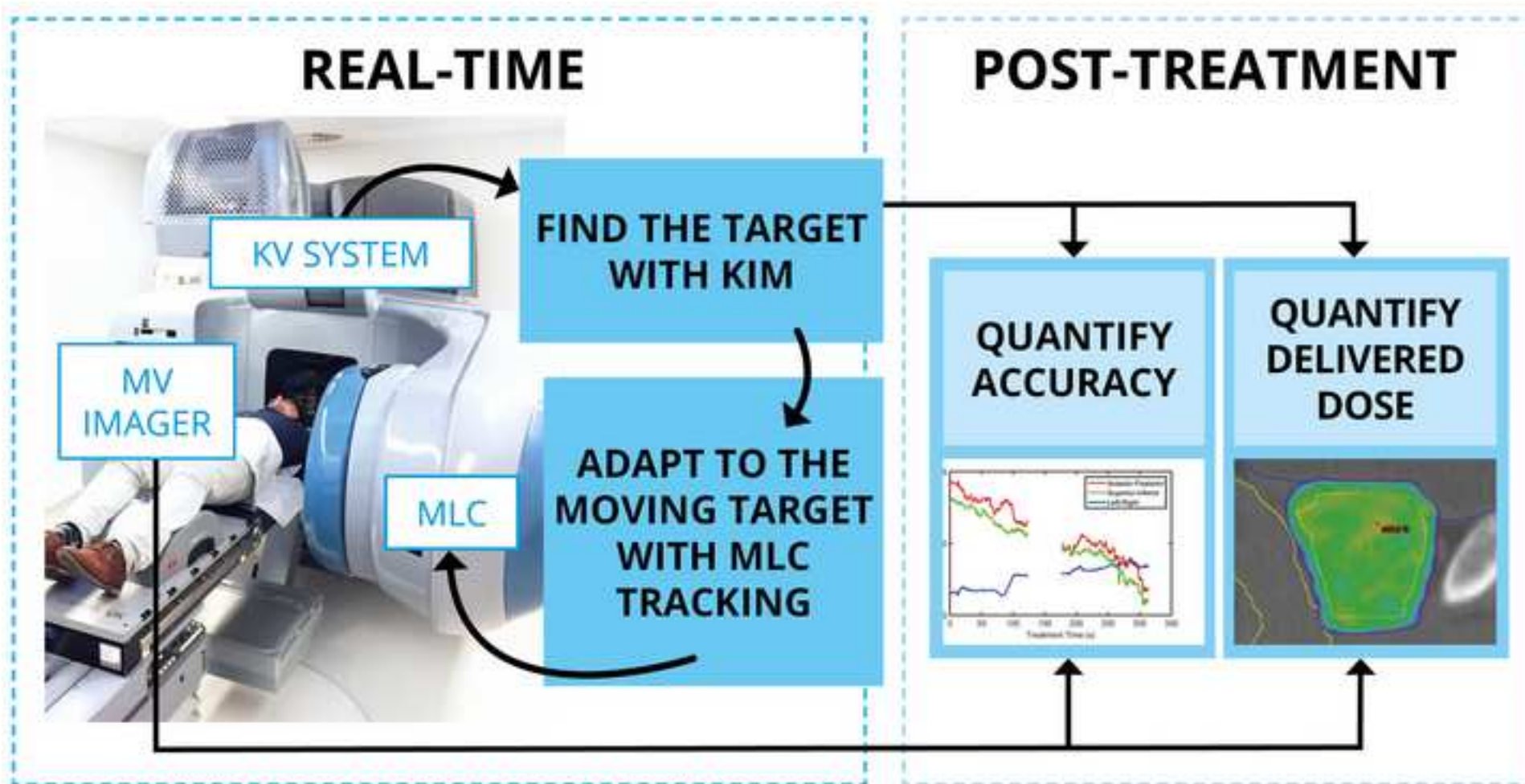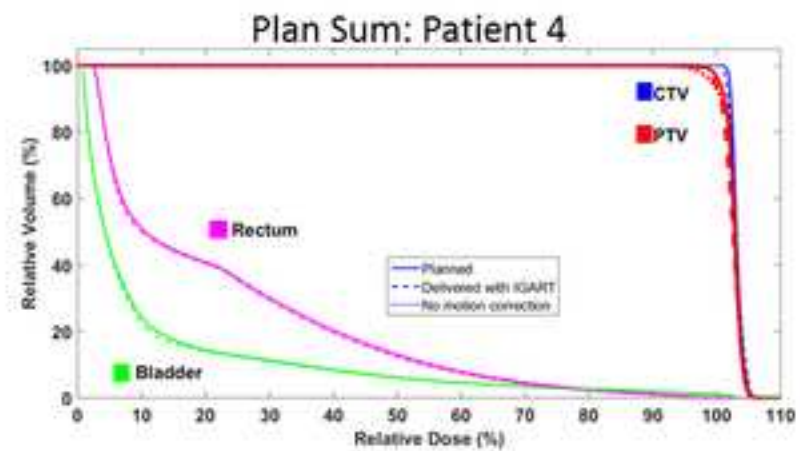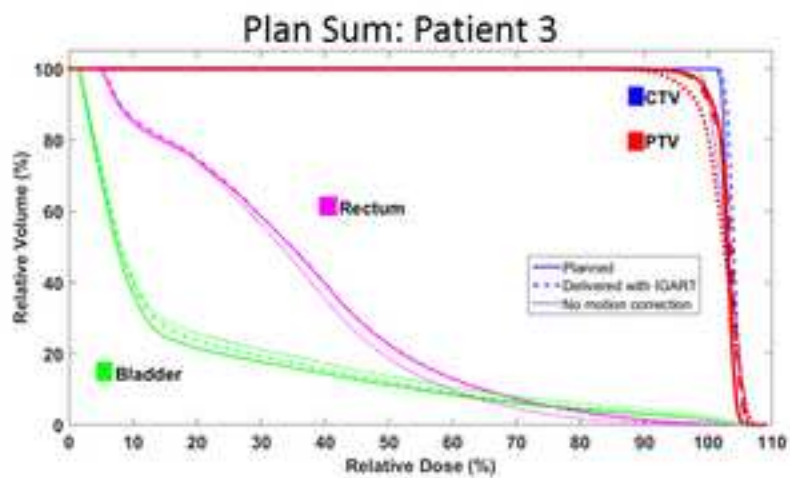
Figure 3
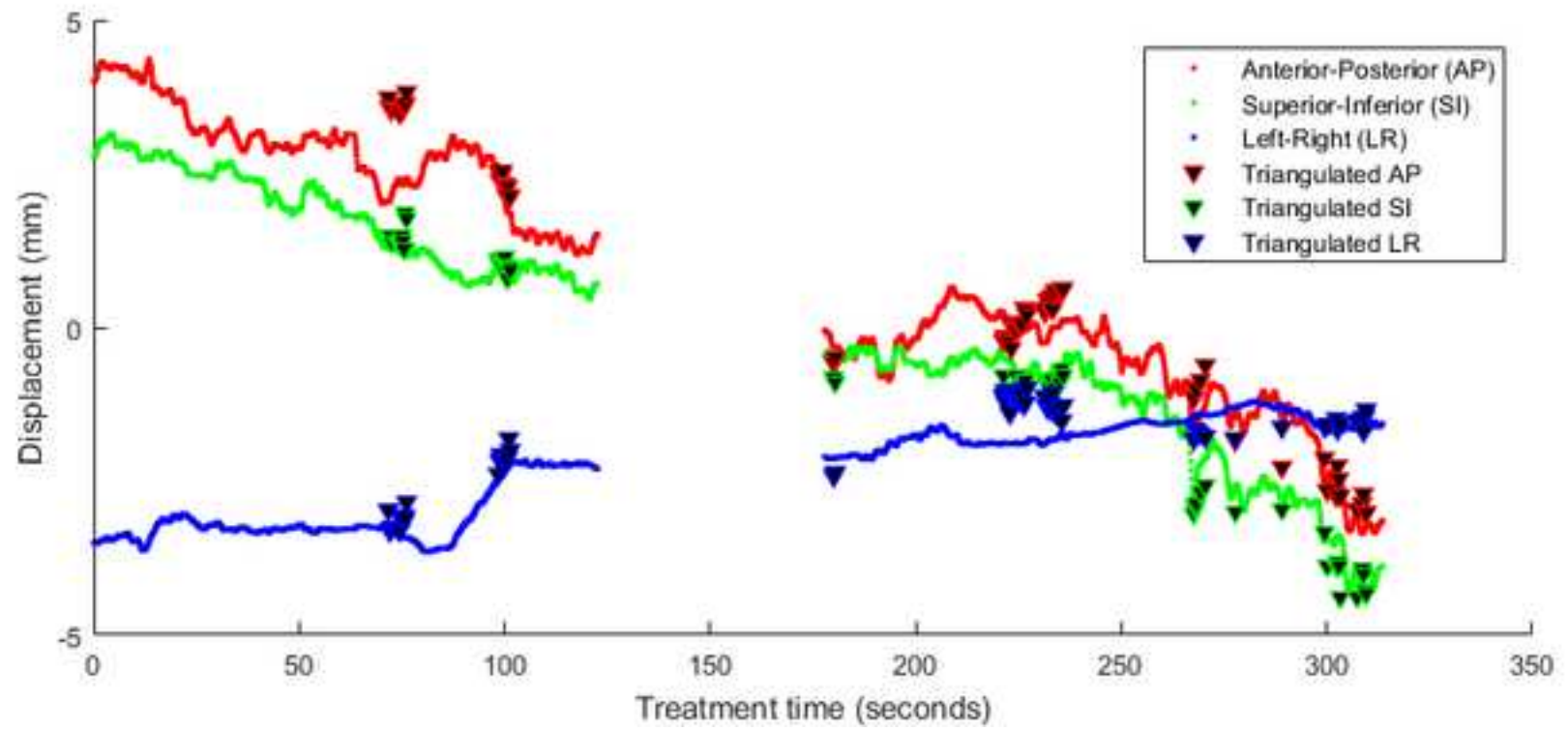**Click here to download high resolution image**

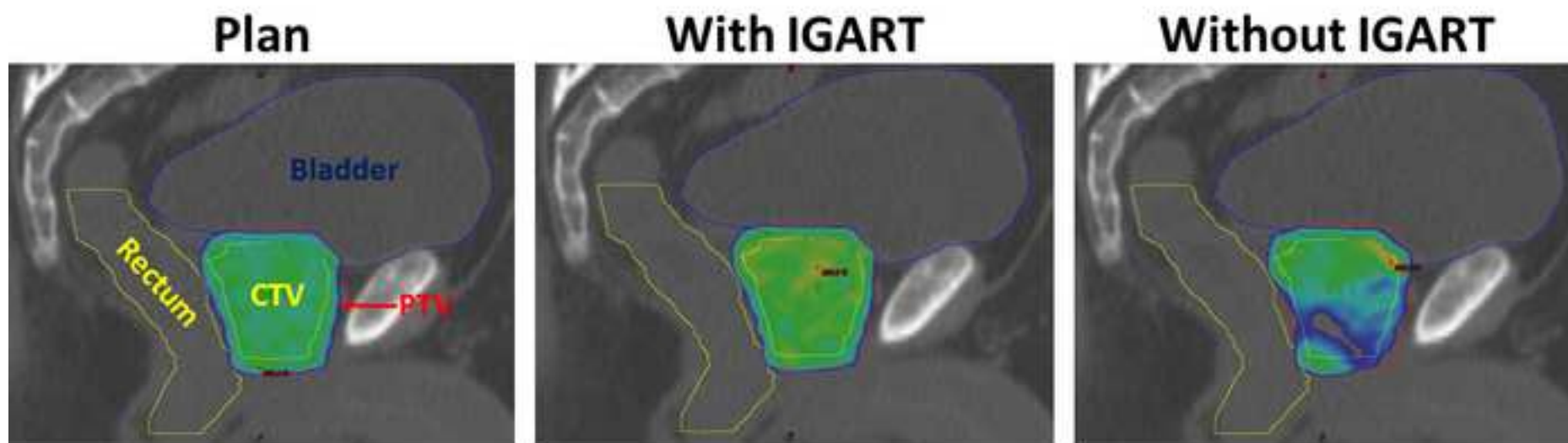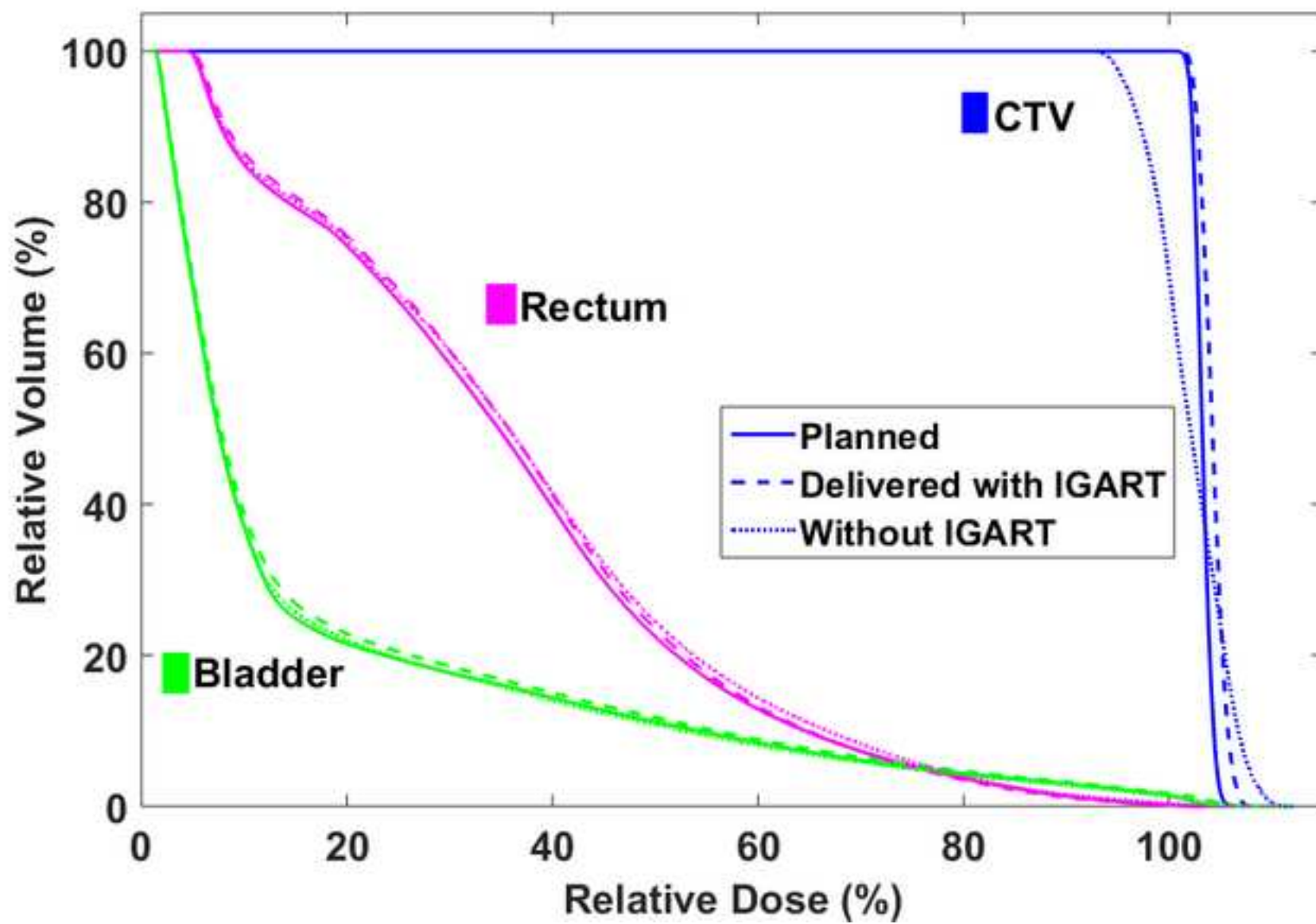**Figure 4**
Click here to download high resolution image

Figure 5
Click here to download high resolution image

Supplementary Files

Click here to download Supplementary Files: KIM_MLC_in_operation_KIM_3.mp4

CONFLICT OF INTEREST STATEMENT