

The First Clinical Implementation of a Real-Time Six Degree Of Freedom Target Tracking System During Radiation Therapy based on Kilovoltage Intrafraction Monitoring (KIM)

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Abstract

Purpose: We present the first clinical implementation of a real-time six-degree of freedom (6DoF) Kilovoltage Intrafraction Monitoring (KIM) system which tracks the cancer target translational and rotational motions during treatment. The method was applied to measure and correct for target motion during stereotactic body radiotherapy (SBRT) for prostate cancer.

Methods: *Patient:* A patient with prostate adenocarcinoma undergoing SBRT with 36.25 Gy, delivered in 5 fractions was enrolled in the study. *6DoF KIM technology:* 2D positions of three implanted gold markers in each of the kV images (125 kV, 10 mA at 11 Hz) were acquired continuously during treatment. The 2D→3D target position estimation was based on a probability distribution function. The 3D→6DoF target rotation was calculated using an iterative closest point algorithm. The accuracy and precision of the KIM method was measured by comparing the real-time results with kV-MV triangulation.

Results: Of the five treatment fractions, KIM was utilised successfully in four fractions. The intrafraction prostate motion resulted in three couch shifts in two fractions when the prostate motion exceeded the pre-set action threshold of 2mm for more than 5 seconds. KIM translational accuracy and precision were 0.3 ± 0.6 mm, -0.2 ± 0.3 mm and 0.2 ± 0.7 mm in the Left-Right (LR), Superior-Inferior (SI) and Anterior-Posterior (AP) directions, respectively. The KIM rotational accuracy and precision were $0.8^\circ\pm 2.0^\circ$, $-0.5^\circ\pm 3.3^\circ$ and $0.3^\circ\pm 1.6^\circ$ in the roll, pitch and yaw directions, respectively.

Conclusion: This treatment represents, to the best of our knowledge, the first time a cancer patient's tumour position and rotation have been monitored in real-time during treatment. The 6 DoF KIM system has sub-millimetre accuracy and precision in all three translational axes, and less than 1° accuracy and 4° precision in all three rotational axes.

Introduction

In current radiation therapy, image guided radiation therapy (IGRT) is routinely applied at the start of treatment to align the target with its planned position. However, tumours in the thorax, abdomen and pelvis are not static during treatment. Hence, methods to monitor tumour motion during treatment are highly desirable, even more so with dose escalation and hypofractionation.

A number of different intrafraction real-time guidance methods have been used during prostate cancer treatments. Systems such as CyberKnife (Accuray, Sunnyvale, CA) and the real-time tracking radiotherapy (RTRT) system, pioneered by Shirato et al. (2000) [1], use real-time kilovoltage (kV) images from two (CyberKnife) or four (RTRT system) orthogonal room-mounted imagers to track the prostate position based on segmented positions of implanted fiducial markers [1-6]. Calypso (Varian, Palo Alto, CA) [7] and RayPilot (Micropos, Gothenburg, Sweden) [8] utilise implanted electromagnetic transponders, transmitting positional signals to an external receiver. Emerging real-time guidance technologies include ultrasonography [9] and integrated magnetic resonance imaging (MRI)-radiation therapy systems [10, 11]. Common to all these methods is the need for additional dedicated and typically expensive equipment to perform the real-time guidance. Ideally, real-time image guidance would be performed using a standard linear accelerator (linac) without relying on additional hardware. Reported to have similar accuracy (sub-millimetre) to the Calypso system is the Kilovoltage Intrafraction Monitoring (KIM) system which estimates tumour position in real-time based on kV images from a single on-board imager (OBI) mounted on a standard linac [12, 13]. The first clinical trial implementing real-time KIM for prostate cancer radiation therapy with beam gating and couch correction to re-align the tumour position with the treatment isocenter was reported by Keall et al. [14, 15].

Currently, all the aforementioned real-time guidance technologies only consider translational tumour motions and not rotational motions in real-time. Specifically, no real-time information on target rotational motion is visible to the user in the Calypso system or the CyberKnife system during prostate treatments. However, increasing evidence suggests that intrafractional tumour motion corrections should be applied to both tumour translations and tumour rotations [16-18]. Off-line post-treatment calculation of tumour rotations have shown that the rotations could be significant for both prostate and lung tumours [16, 19]. Dosimetrically, uncorrected prostate rotations of 15° can result in a 12% under dose to the tumour [17]. Tumour rotation estimation using KIM has been developed using the iterative closest point (ICP) approach [20]. This method has been used retrospectively to quantify translational and rotational motion for prostate and lung cancers [21]. However, until the current study the method had not been used in a prospective clinical trial.

In the present work, we describe the first clinical implementation of a real-time six degree of freedom motion monitoring system based on KIM (6 DoF KIM). We also report on the geometric and dosimetric results of the first patient treatment using 6 DoF KIM which occurred in February and March 2016 at the Calvary Mater Newcastle Hospital (Waratah, New South Wales, Australia).

Methods

All necessary ethical, legal, and regulatory requirements were met, including filing a clinical trial notification with the Australian Therapeutic Goods Administration. The patient was enrolled on a clinical trial under the auspices of the Trans-Tasman Radiation Oncology Group (TROG 15-01: SPARK – ClinicalTrials.gov identifier NCT02397317). Human Research Ethics Committee (HREC) approval was provided by the Hunter New England HREC (Reference number 15/06/17/3.01).

Patient characteristics

A male patient, aged 57 with baseline PSA of 5.8 and biopsy confirmed prostate adenocarcinoma (Gleason score 3+4=7, Grade group 2/5, stage T2aN0M0), provided informed consent to participate in the study. He had previously commenced a six month course of adjuvant androgen deprivation therapy. The patient was implanted with three intraprostatic gold markers (1 mm \varnothing \times 3 mm length). He underwent stereotactic body radiotherapy (SBRT) with 36.25 Gy delivered in 5 fractions using dual arc RapidArc on a Varian Truebeam Linac with 6MV energy. His PTV margin from the prostate CTV was 5 mm in all directions except posteriorly where the margin was 3 mm.

KIM 6DoF implementation: rotation and translation

The core of the KIM method is the 2D to 3D transformation first described by Poulsen et al in 2008 [13]. KIM estimates the 3D position of each implanted marker based on segmented 2D marker positions in each of the kV images taken continuously during the arc. This transformation relies on motion confinement and the correlation of motion between the observed and unobserved directions. The 2D \rightarrow 3D target estimation is based on a probability distribution function (pdf) determined via maximum likelihood, obtained during pre-treatment CBCT.

Rotations of the triangle formed by the three markers about each axis with the centroid of the markers as the pivot were calculated using the iterative closest point algorithm as described in [20]. In the present implementation, the rotations of the tumour about all three axes were calculated as soon as 3D position of the each marker position became available through KIM 2D-3D estimation. Rotations were computed with the positions of the implanted fiducials from the planning CT as reference. A five point averaging filter was used to smooth out the rotation output prior to display.

Clinical process

KIM does not require any additional hardware to be installed in the treatment system. The KIM software is installed in a computer which also runs the CDOG framegrabber software (Calvary Mater Hospital, Newcastle). The framegrabber is connected to the OBI through a pair of frame grabbing cables. This way, fluoroscopic and CBCT projection images acquired by the OBI are streamed directly to the KIM software, giving KIM real-time capability.

Before treatment, a text file with the treatment isocenter 3D location and the 3D locations of each implanted marker was exported from the Eclipse planning system. This file also contains the patient's name and medical record number (MRN). Prior to treatment, the file with patient data is read into the KIM software. For safety, the patient's name, MRN, and picture are compared to those on the treatment console as currently there is no communication between the KIM computer and the treatment console. The current couch position is manually entered to guide correction in the case of a gating event. The planned marker positions are used to define the initial search region for the marker detection software and are employed throughout the treatment for safety checks. The planned markers positions are also used by KIM to resolve events where markers overlap during the learning phase. After the segmentation template has been built and the 3D pdf of each marker has been computed, marker overlapping events are handled by switching to a joint template for two or more markers within the field of view.

After the patient was set-up with the treatment room lasers, a kV-kV pair match was performed to align the tumour with the treatment isocenter. A CBCT (full fan, half trajectory) was then acquired to check the patient's day-to-day anatomical changes. During CBCT, the KIM software also learnt the marker positions and built the 3D pdf for each marker.

During treatment, kV images were continuously acquired at 11 Hz while the treatment MV beam was on. The imaging parameters were 125 kVp and 10 mA (15 ms) with a field size of $6\times 6\text{ cm}^2$. The additional absorbed dose to the patient for the entire course of treatment due to intrafraction imaging was 0.3 Gy, equivalent to 0.7% of the prescribed dose, based on experimental results in Crocker et al.'s study [22], adjusting to the aforementioned imaging parameters and 300 seconds of beam on time. As KIM uses the temporal average of every three images to mitigate MV scatter on the kV imager, the total processing time for each incoming image is 0.27 ± 0.05 seconds.

The KIM system enabled users to observe the prostate translational and rotational motion in real-time, as shown in Figure 1. When the prostate target translational motion exceeded the pre-set action threshold ($>2\text{ mm}$ in any direction), the system signalled a WARNING (Figure 1). If the motion exceeded the threshold for more than 5 seconds, a BEAM OFF signal was given. KIM then calculated the couch shifts required for target re-alignment. As there was no direct link between KIM and the treatment system, a manual beam pause was performed by the radiation therapist. With the Varian TrueBeam system, a couch shift could only be executed by kV-kV match or CBCT during treatment. Thus, as the beam was paused, a kV-kV match was carried out. The couch was shifted according to KIM's output and the shifts confirmed by radiation therapists by manual matching. In the current protocol, if the shifts output by KIM are more than 2 mm away from the therapist manual match, the couch will be shifted to the therapist's match values because they reflect a more recent target position. In that case, a new couch position could be entered into KIM.

Rotational motions of the target were also utilised. At the conclusion of pre-treatment CBCT, if KIM detected large target rotation of more than 15° in any rotational axis, the patient would be re-positioned manually with the assistance of a therapist. Subsequently, another CBCT would be performed to confirm correction positioning prior to treatment.

Performance analyses

Post-treatment, the real-time 6DoF KIM accuracy and precision were measured by comparing the results with kV-MV triangulation measurements of the marker positions. The positions of each of the fiducial markers as estimated by KIM during treatment were compared with the triangulated positions in the MV image frames that the marker was visible. Thus, for the translational accuracy, the analysis was drawn on the statistics of each individual marker. However, for the rotational accuracy, as three markers were required to calculate rotations, the analysis required MV frames with all three markers visible.

The performance of KIM-guided gating to deliver the planned dose was measured using an isocenter shift dose reconstruction method [23]. The delivered dose was reconstructed on the planning CT using the intrafraction prostate motion trajectories and linac trajectory log files, and compared directly against the planned dose.

Results and Discussion

The first intrafraction six degree of freedom motion monitoring system based on KIM was successfully applied clinically to treat a prostate cancer patient with beam gating and couch shift corrections.

Intrafraction prostate motions

Of the five treatment fractions, KIM was utilised successfully in four fractions with a total of three gating events with couch corrections. The target rotations were under the action threshold in all fractions, thus, no manual patient correction was required for the patient. In one fraction (fraction 4), KIM was aborted due to a segmentation error at the beginning of the first treatment arc.

In two of the four KIM fractions, the prostate had a stable position throughout the treatment. In one fraction, there was a slow drift in the SI direction, culminating in a couch shift toward the end of the first arc; prostate rotations were not affected by couch shifts. One fraction had erratic motion, requiring two couch shifts (total shift of -5.5 mm SI, -6.0 mm AP and 0.6 mm LR) (Figure 2). Additionally, the prostate rotation in this fraction was also similarly erratic, especially in the pitch and roll (Figure 2). Comparing post treatment CBCT with pre-treatment CBCT showed a large bladder filling occurring during the fraction.

KIM performance

KIM translational and rotational accuracy (mean) and precision (standard deviation) in comparison with post treatment kV-MV triangulation is shown in Table 1. The analysis was based on 680 MV image frames in which at least one fiducial marker was visible. KIM has sub-millimeter accuracy and precision in all translational axes, based on 1005 individual data points. For the three axes of rotation, KIM accuracy is within 1° while the precision is under 4° , based on 18 frames in which all three markers were visible.

The KIM translational accuracy and precision in this study are consistent with previous studies [12, 14].

Table 1. KIM mean (accuracy) and standard deviation (precision) error compared with kV-MV triangulation.

Motion	Mean	Standard deviation
Left-Right	0.3 mm	0.6 mm
Superior-Inferior	-0.2 mm	0.3 mm
Anterior-Posterior	0.2 mm	0.7 mm
Roll	0.8 °	2.0°
Pitch	-0.3°	3.3°
Yaw	0.3°	1.6°

Dosimetric results

As intuitively expected, the treatment adaptation strategy of beam gating and couch shift enabled by KIM provided the most dosimetric advantage when there were large prostate motions. In the fraction with the erratic motion, the prostate moved mostly anteriorly and superiorly (6 mm AP, 5.5 mm SI). The couch shifts corrected for this motion and provided superior dose coverage to that which would have been delivered with no motion correction (Figure 3).

Table 2 shows the total dose delivered to the target and organs at risk over all five fractions of treatment with KIM, compared to motion correction (estimated) and the planned dose, assuming that the dose delivered in the fraction that KIM was not utilised was as planned. The Dose Volume Histogram (DVH) of each delivered fraction and summation of the treatment course are shown in Figure 4.

Table 2. Total dose delivered to patient with KIM and without motion correction.

Dose-volume value	Plan	Delivered with KIM	Estimated without motion correction
CTV D2%	38.0 Gy	38.1 Gy	38.0 Gy
CTV D98%	36.0 Gy	36.3 Gy	36.1 Gy
PTV D95%	36.3 Gy	35.8 Gy	35.4 Gy
Rectum V50%	28.3%	28.5%	29.3%
Bladder V50%	25.2%	24.4%	22.9%

Translational relevance

This paper describes the first time internal target translation and rotation motion has been measured in real-time during a clinical radiotherapy treatment using only a standard linac. This milestone represents a tremendous effort by a large team that is required to overcome the ‘valley of death’ described in the *First in Man* editorial [24]. Many promising discoveries never find their way into clinical application simply because the barrier is too high. For these bench-to-bedside studies, treating the first patient is often the biggest milestone. All of the physics, mathematics, software development, clinical processes, training, quality assurance, ethics, legal and regulatory framework needs to be completed and at a point where the entire team is comfortable with the implementation of the new technology. In addition the physician and the patient need to believe in the benefits of the technology sufficiently that they agree to participate and trust their care to the technology and the team delivering it. As with the other papers published in the *First in Man* category of Radiotherapy and Oncology [25-27], the

first clinical implementation changes technology from being an abstract physics concept to a clinical reality.

Clinical Implications

The presented KIM system is, to the best of our knowledge, the first clinical use of a real-time intrafraction tumour target tracking that provides six degree of freedom motion information. Importantly, this milestone has been achieved with the commonly available monoscopic gantry mounted OBI, rather than expensive third party systems such Calypso or Cyberknife. Thus, there is a streamlined and cost-effective pathway for the broader dissemination of real-time six degree of freedom target tracking for widespread patient use during radiation therapy.

The translational movements are currently used for treatment adaptation by means of couch shifts, allowing better precision in treatment delivery particularly for high dose fractions. The rotational motion provided by KIM in real-time allows large rotation differences between planned and actual target positions to be corrected, and opens up possibilities for real-time rotation correction strategies such as MLC adaptation [18, 28], or couch rotation.

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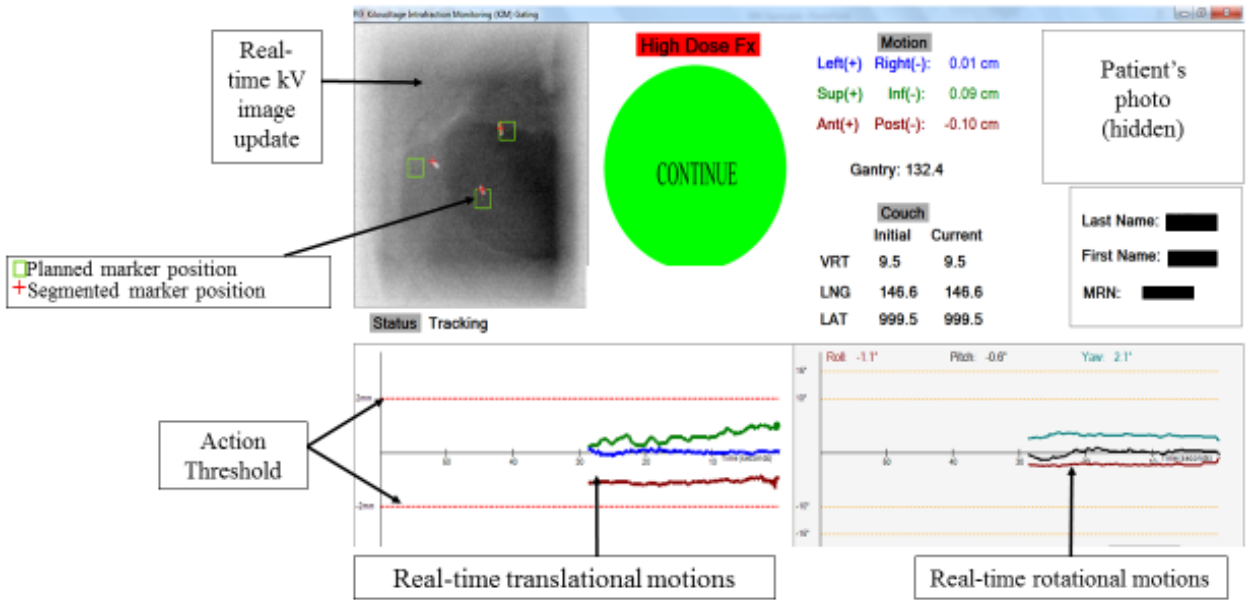


Figure 1. KIM 6 degree-of-freedom software interface showing the real-time image, marker segmentation, and real-time six degrees of freedom motion.

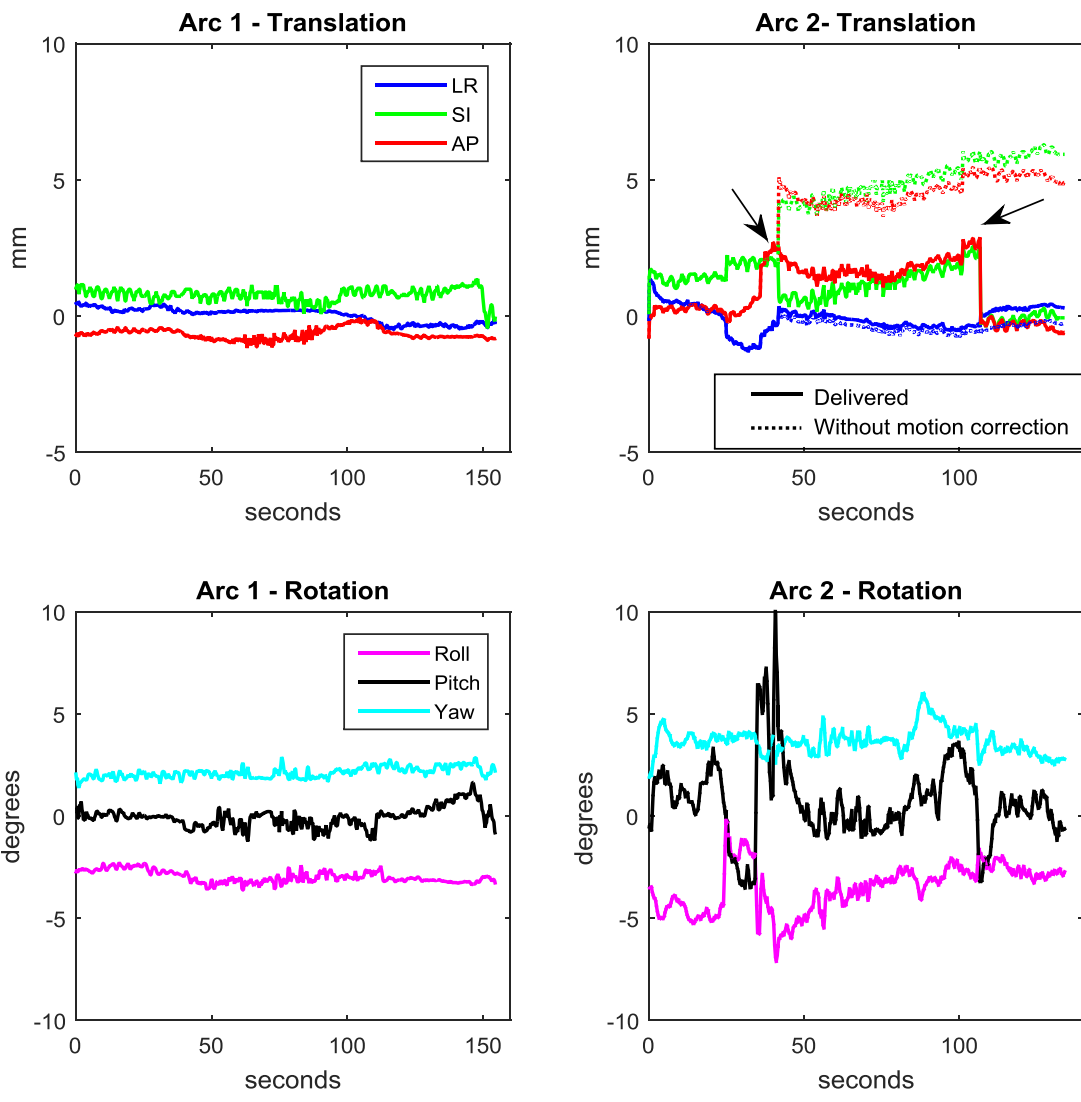


Figure 2. Patient prostate motion for the fraction with the largest motion, resulting in two couch shifts in the second arc, indicated by black arrow in the translational motion plot. The rotational motion was within tolerance and therefore not corrected.

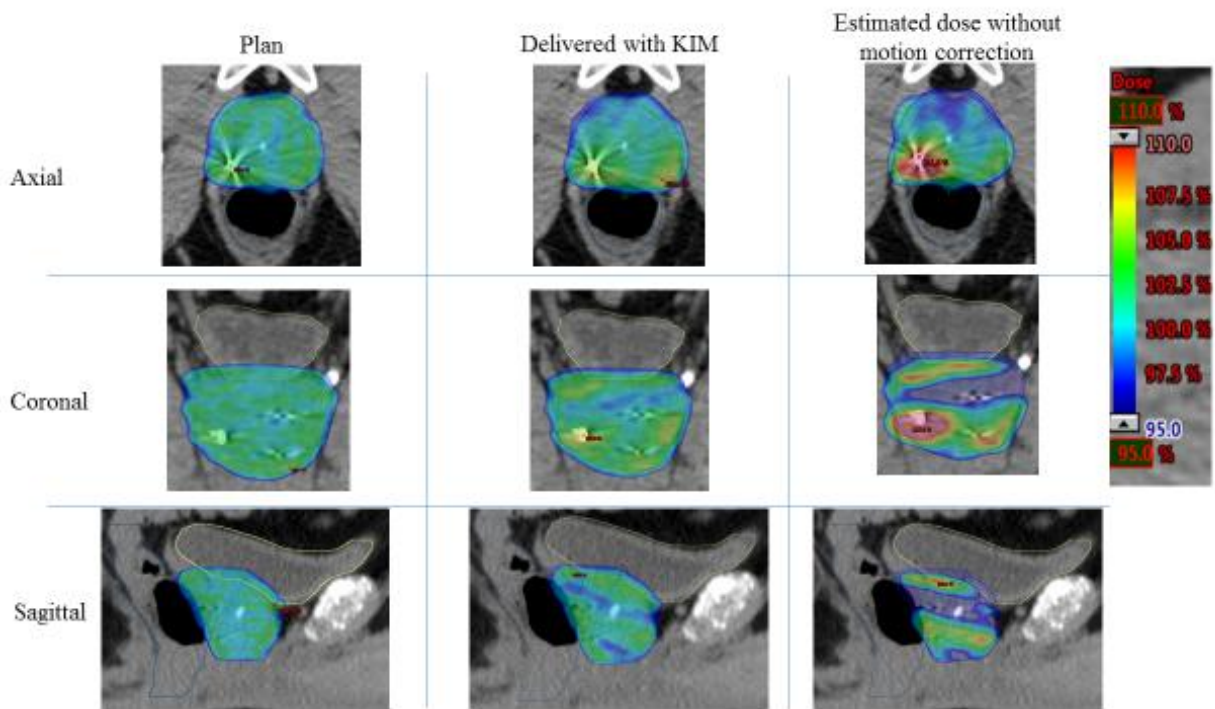


Figure 3. Dose wash of the dose reconstruction for the fraction with the largest motion with and without correction, comparing to the planned dose distribution. The prostate (red), rectum (blue) and bladder (yellow) are contoured.

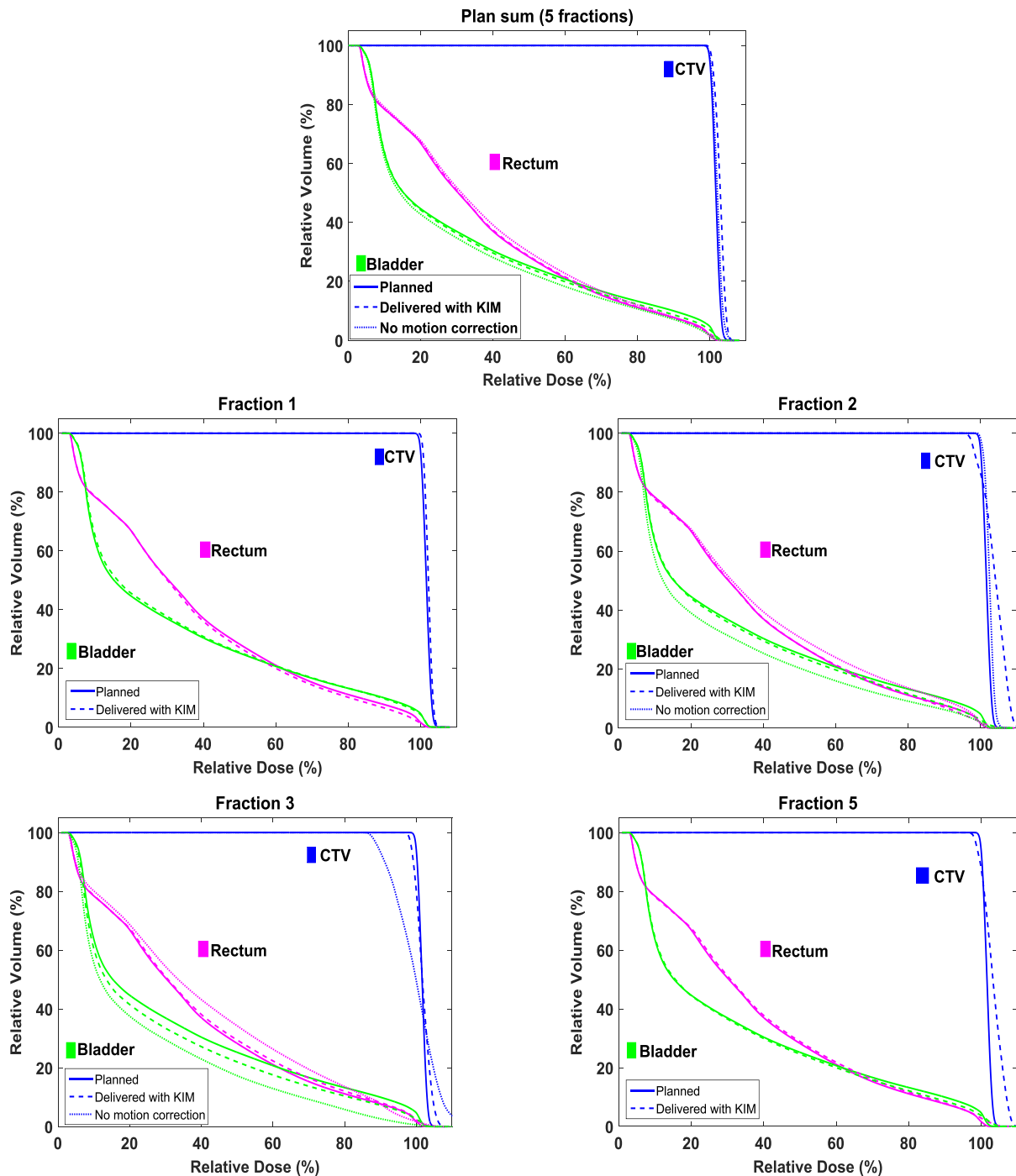


Figure 4. Dose Volume Histograms of treatment plan (solid line), compared with dose reconstructions for delivered with KIM (broken line) and without KIM correction (dotted line) using KIM acquired tumour motion for each successful fraction and the total course of treatment. In fractions without any couch shift, only the delivered dose is reported. In fraction 2, a couch shift was applied to correct for target slow drift motion in the SI direction (+2 mm); however, after the shift, the target moved in the opposite direction of the shift and remained stable for the rest of treatment (-1 mm SI). Consequently, the dose reconstruction result for fraction 2 indicated a better dose coverage could have been achieved without any motion correction.

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Conflict of Interest Statement

With regard to conflict of interest, authors Poulsen and Keall are inventors of a patent that has been licensed to Varian Medical Systems by Stanford University, and authors O'Brien, Poulsen and Keall are inventors of a separate unlicensed patent.

No other listed author has any conflict of interest.