Real-time 3D image guidance using a standard linac: Measured motion, accuracy and precision of the first prospective clinical trial of kilovoltage intrafraction monitoring (KIM)-guided gating for prostate cancer radiotherapy

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Conflicts: Authors Keall and Poulsen are inventors on an issued US patent on the KIM technology that has been licensed from Stanford University to Varian Medical Systems. Varian Medical Systems have provided an equipment loan for this study.

Summary

Kilovoltage intrafraction monitoring (KIM) is a new real-time 3D image guidance method. Unlike previous real-time image guidance methods, KIM uses a standard linac without any additional expensive equipment needed. The first clinical trial of KIM is underway for prostate cancer radiotherapy. Results from the first 200 treatment fractions show that KIM-guided gating eliminates large prostate displacements during treatment delivery. The KIM accuracy and precision are both well below one millimeter.

Abstract

Purpose:

Kilovoltage intrafraction monitoring (KIM) is a new real-time 3D image guidance method. Unlike previous real-time image guidance methods, KIM uses a standard linac without any additional equipment needed. The first prospective clinical trial of KIM is underway for prostate cancer radiotherapy. In this paper we report on the measured motion accuracy and precision using real-time KIM-guided gating.

Method and Materials:

Imaging and motion information from the first 200 fractions from six patient prostate cancer radiotherapy VMAT treatments were analyzed. A 3 mm/5 second action threshold was used to trigger a gating event where the beam is paused and the couch position adjusted to realign the prostate to the treatment isocenter. To quantify the *in vivo* accuracy and precision, KIM was compared with simultaneously acquired kV/MV triangulation for 187 fractions.

Results:

KIM was successfully employed in 197 of 200 fractions. Gating events occurred in 29 fractions (14.5%). In these 29 fractions, the percentage of beam-on time the prostate displacement was >3 mm from the isocenter position was reduced from 73% without KIM to 24% with KIM-guided gating. Displacements >5 mm were reduced from 16% without KIM to 0% with KIM. The KIM accuracy was measured to be <0.3 mm in all three dimensions. The KIM precision was <0.6 mm in all three dimensions.

Conclusions:

The clinical implementation of real-time KIM image guidance combined with gating for prostate cancer eliminates large prostate displacements during treatment delivery. The *in vivo* KIM accuracy and precision are both well below 1 mm.

Introduction

There is a history of improvements in radiotherapy technology improving cancer treatment outcomes. These advances are particularly evident for prostate cancer where two technologies, intensity modulated radiotherapy (IMRT) [1] and pre-treatment image guided radiotherapy (IGRT) [2], have demonstrated improved tumor control and lower rates of late rectal toxicity. However, even with IMRT and IGRT, intrafraction prostate motion during radiotherapy can simultaneously reduce the target dose and expose normal tissues to potentially damaging radiation doses. To address the intrafraction motion problem, an evolving class of technologies, real-time image guidance, has demonstrated lower toxicity in a matched-pair analysis [3] and dosimetric improvements [4,5] for prostate cancer.

A number of different real-time image guidance methods have been used to treat prostate cancer patients including the Real-time Tracking Radiotherapy system [6], CyberKnife linear accelerators (frequent x-ray imaging during treatment) [7], Calypso [8], Navotek [9] and RayPilot [10]. Emerging real-time guidance technologies include ultrasound [11] and integrated MRI-radiotherapy systems [12-14]. Common to all of these methods are the need for additional dedicated and typically expensive equipment to perform the real-time guidance. Ideally, real-time image guidance would be performed on a standard linear accelerator with little modification required. A new real-time image guidance technology, kilovoltage intrafraction monitoring (KIM) [15], uses the gantry-mounted x-ray imaging system of a standard linac to image and detect the 3D positions of implanted markers. The first clinical treatment with real-time KIM occurred in 2014 [16]. Other than a description of the first fraction with KIM [16], there have been no reports of the prospective use of this real-time image guidance technology.

In this paper we investigate and quantify the measured motion, accuracy and precision of the first 200 treatment fractions of real-time KIM-guided gating for prostate cancer radiotherapy.

Method and Materials

The KIM method

The KIM theory [17], retrospective clinical results for prostate [18] and liver [19], dose assessments [20,21], quality assurance procedure [22] and the description of the first treatment fraction [16] have been previously published. The KIM steps are (1) kV imaging during MV treatment, (2) prostate gold marker segmentation in the 2D images, (3) 2D→3D reconstruction using maximum likelihood based on estimated motion correlations and (4) display of the real-time 3D position. KIM reads images from the gantry-mounted x-ray imager and processes them in real time via steps 1-4 above.

The KIM deployment was implemented according to the protocol described in [18], with all patients imaged at 10 Hz and the KIM implementation performed in real-time, with gating corrections as opposed to the retrospective implementation in [18]. Briefly, the protocol for this trial used 10 Hz kV imaging at 125 kVp, 80 mA, 13 ms with a 6×6 cm^2 field size. A 120-degree pre-treatment imaging kV imaging arc was used to build the probability density function. After gating events, and prior to treatment initiation, a 5 second kV imaging sequence was delivered to check if the prostate was still in the gated position. The kV beam was on throughout the MV treatment delivery to provide the real-time guidance. The estimated dose is 0.7 Gy for a 40 fraction treatment, based on the Crocker study [21], adjusting for increased imaging frequency (10 Hz not 1 Hz) and decreased average treatment time (100s not 200s of beam on). Monthly quality assurance (QA) for KIM followed Ng *et al.* [22]. Patient-specific QA used standard patient-specific VMAT procedures, and in-house developed clinical processes to ensure the correct data for the correct patient was used for each treatment.

Examples of the clinical user interface when motion is within tolerance, and when motion has exceeded tolerance and a couch shift is required are shown in Figure 1. Note that for the current version of the software, couch shifts need to be manually performed as an automatic gating interface has yet to be developed and would need additional regulatory approval for clinical use.

Patient cohort

Six patients provided written informed consent in this ethics-approved trial (NCTxxxx). The patients had biopsy confirmed prostate cancer from AJCC clinical stage T1c to T2. All patients had 3 gold seeds (4.5 mm length, 1.0 mm diameter) implanted into the prostate, were planned with dual-arc VMAT and treated on a Trilogy (Varian) linear accelerator. Patients were treated to 80 Gy in 2 Gy fractions. CTV to PTV margins were 7 mm except 5 mm posteriorly. Departmental bowel and bladder filling protocols [23] were followed. The time from the pre-treatment imaging arc to the end of the last treatment beam was 209 ± 50 (range 145-430) seconds.

With KIM monitoring, if prostate motion ≥3 mm in any of the three dimensions was observed for ≥5 seconds, the treatment was paused and the couch position altered to move the prostate back to be aligned with the beam based on the latest measured position. The 3 mm/5 second threshold was based on the results of a dose reconstruction study that showed the CTV D_{99} is within 4% of the planned dose with this action threshold [24]. The first 200 fractions have been analyzed for this study.

Exclusion criteria for the current version of the KIM software include a lateral pelvic width >40 cm, overlapping markers in the axial plane and any hip prosthesis.

Motion measurements

The KIM software logs the 3D (anterior-posterior, superior-inferior and left-right) positions of each of the markers during treatment, enabling the prostate motion to be quantified. When gating events occur, couch shifts are recorded. The magnitude of the couch shifts enables estimation of the motion that would have occurred in the absence of real-time guidance.

Accuracy and precision measurements

To quantify the accuracy and precision of KIM *in vivo*, the real-time KIM patient motion measurements were compared with simultaneously acquired kV/MV-derived marker triangulation results which were considered the ground truth. Triangulation was performed by determining the 3D intersection of the line between the source and marker position on the MV images and the line between the source and marker position on the kV images. The method is shown schematically in

Figure 2. The difference between the individual markers determined with KIM and kV/MV triangulation were recorded. For the measurements the accuracy (mean difference) and precision (standard deviation of the differences) were determined.

For post-treatment analysis the MV imager was employed to acquire intra-treatment EPID images for 187 of the 200 fractions. Based on these images, kV/MV triangulation was performed after each fraction to use as a benchmark for the KIM accuracy. Due to the VMAT MLC modulation and poorer MV image contrast, the markers were not visible in all MV images. However at least one marker was visible in ~11% (i.e. 18,577 of 177,650 total) images, with between 40 and 203 images per fraction available for analysis.

After the first 80 fractions, small systematic errors were observed. By adjusting the KIM calibration, these errors were reduced.

Results

Motion measurements

KIM was used successfully in 197 fractions of 200 attempted fractions. The failure in the three fractions was due to the operators not adhering to the documented clinical process required to enable kV imaging during MV treatment and intra-treatment couch shifts. When KIM failed, the patients were treated with the standard of care (IGRT without real-time guidance). Of the 200 fractions, KIM-guided gating events per the 3 mm/5 second criteria occurred in 29 fractions (14.5%). The largest motion observed was 11.7 mm.

An example of KIM measured motion during a fraction with gating events is given in

Figure 3a. For this patient, two gating events were detected with couch corrections, at 35 seconds and before Arc 2. Almost all of the motion is within 3 mm. The prostate motion that would have occurred in the absence of real-time guidance is shown in

Figure 3b. The prostate motion exceeds 5 mm for most of the treatment.

The percentage of beam on time that the 3D prostate motion with respect to the isocenter was within a given motion value with and without KIM-guided gating for all fractions is shown in Figure 4. Also plotted is the subset of measured motion for the 29 fractions with the gating events, and the estimated motion for these fractions had no real-time monitoring or gating been used.

Accuracy and precision measurements

The difference between the KIM and kV/MV triangulation measurements for patient 4 is shown in Figure 5. The measurements show that the accuracy (mean error) and precision (standard deviation of error) were below 1 mm. Summary accuracy and precision measurement statistics for all patients and fractions are shown in Table 1. We investigated the correlation between the 3D root mean square (rms) error and the mean 3D motion within each fraction. We observed a correlation of 0.01 ($p = 0.09$) indicating that the observed errors are independent of the KIM-measured motion.

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Discussion

Given the complexity of prostate motion, Ballhausen *et al.* [11] conclude "fixed safety margins (which would over-compensate at the beginning and under-compensate at the end of a fraction) cannot optimally account for intra-fraction motion. Instead, online tracking and position correction on-the-fly should be considered as the preferred approach to counter intrafraction motion." In the current paper we report on the clinical implementation of a new online tracking method, kilovoltage intrafraction monitoring (KIM), on a standard linac. Given the wide availability of standard linacs, and the routine use of implanted gold markers for prostate cancer IGRT, this makes real-time guidance, and the associated clinical benefit [3-5], potentially broadly accessible to cancer patients.

KIM–guided gating reduced the prostate displacements. For the fractions with gating events, the percentage of beam-on time the prostate displacement was >3 mm from the isocenter position was reduced from 73% without KIM to 24% with KIM-guided gating (Figure 4). Displacements >5 mm were reduced from 16% of the time without KIM to 0% with KIM. Particularly noticeable is the

elimination of the large displacements, which have the highest negative dosimetric impact on the treatment dose [24].

The prostate motion measured here is similar to that reported by Su *et al.* [25] using a comparator technology, Calypso. From 17 patients Su *et al.* found a 3D prostate displacement of ≥3 mm for 20% of the time (Figure 1 in their paper) which is similar to the 18% observed for the KIM cohort presented here in Figure 4.

The clinically determined accuracy of the KIM method, as determined from the kV/MV triangulation (Figure 5 and Table 1), demonstrates sub-millimeter accuracy and precision, indicating that the error in the KIM system is well below other errors in the radiotherapy process, such as the organ motion itself and prostate contouring variability. The clinically determined accuracy and precision measurements are consistent with those determined during commissioning and quality assurance procedures [22].

The most widely used clinical real-time prostate monitoring system is Calypso (Varian). KIM compares favorably to Calypso in many aspects. KIM uses gold markers that are in standard use for IGRT. These are smaller, easier to implant, less costly and more MRI-compatible than those used for Calypso. A disadvantage of KIM is the additional x-ray imaging dose required for monitoring. This dose is a function of many parameters, including the imaging frequency, the acquisition settings, the patient size, and field size [20,21]. Several strategies have been proposed to reduce the imaging dose [18] and are the subject of ongoing development. A potential advantage of using the x-ray images, still to be explored, is the reconstruction of the intra-treatment volumetric patient geometry which would aid in estimating the anatomy during treatment for prostate and risk organ dose accumulation estimates.

Further limitations of the current KIM version are the exclusion criteria which include a lateral pelvic width >40 cm, overlapping markers in the axial plane and any hip prosthesis. Approximately half of the potential patients were excluded. The pelvic width limitation could be overcome by improved image processing and marker segmentation, as well as by allowing an increased dose per image, with a lower frame rate so as not to increase the overall patient dose. The overlapping marker limitation, which was the highest cause of exclusion, can be overcome by

determining the angles where the overlap in the axial plane occurs, and using other angles to build the KIM motion model. Accounting for hip prostheses will likely be a compromise in which treatment angles where the beam aligns with the hip prostheses will be areas where no motion information is possible, with 3D information available during other beam angles. As the AAPM Task Group 63 report [26] suggests that beam arrangements that avoid the prosthesis should be considered first, this limitation may be easily overcome for most patients with prostheses.

The KIM system is in-house written software, and not fully integrated with the treatment delivery system. Thus there are additional overheads for the treatment process, such as software initialization, patient verification and couch correction methods that take additional time compared to a treatment without KIM-guided gating. This additional time is sufficiently short (1-3 minutes) that it has not impacted the 15 minute time slot scheduled for conventionally fractionated prostate patients.

The promising results of the KIM clinical trial to date, summarized in this paper, have encouraged a number of future directions. These include the TROG SPARK trial (NCTxxxx) a multicenter prospective trial testing the use of KIM in prostate cancer patients being treated with Stereotactic Body Radiotherapy (SBRT). The use of KIM for other cancer sites, such as lung and liver, is being explored in clinical pilot studies. As rotation as well as translation is emerging as an important parameter determining dose delivery accuracy and margins [27], the use of KIM to measure rotation to enable real-time 6-degree of freedom image guidance is an active area of research and development [28,29]. With the clinical realization of MLC tracking [5] the integration of KIM with this technology will enable real-time tracking and adaptation on a standard linear accelerator without additional expensive equipment.

Conclusion

The early results from the first clinical implementation of the novel KIM real-time image guidance method have been obtained. When combined with a gating strategy, KIM eliminates large (>5mm) prostate displacements during treatment delivery. The *in vivo* KIM accuracy and precision are both well below 1mm.

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Figure 1. (a) The KIM user interface when motion is within tolerance. (b) The KIM user interface when motion has exceeded tolerance and a couch shift is required. The kV image in the top left of each panel shows the real-time acquired kV image overlaid with the marker positions expected from planning (green squares) and the real-time detected marker positions (red).

Figure 2. The accuracy and precision were determined by comparing the motion detected in real time by KIM with kV-MV triangulation analyzed post-treatment. kV = kilovoltage; MV = megavoltage; KIM = kilovoltage intrafraction monitoring.

Figure 3. (a) Prostate displacement measured with KIM-guided gating. (b) Prostate displacement estimated without KIM-guided gating. For KIM-guided gating couch corrections occurred at 60 seconds (during arc 1) and 170 seconds (before arc 2). The gray shading indicates when the MV beam was turned on. A-P = anterior-posterior; S-I = superior-inferior; L-R = left-right.

Figure 4. Distribution of 3D prostate displacement with respect to the isocenter during beam-on time with and without KIM-guided gating. All fractions and those with gating events are shown. Motion > 3mm was observed for KIM-guided gating as the gating threshold of >3mm of motion for >5 seconds was for motion in any one direction, not the 3D motion. KIM = Kilovoltage intrafraction monitoring; Fx = fraction.

Figure 5. Geometric accuracy results for patient 4 demonstrating sub-mm accuracy (mean error) and precision (standard deviation of error). S-I = superior-inferior; A-P = anterior-posterior; L-R = left-right.

Table 1. Accuracy and precision measurements over all fractions and patients comparing KIM with kV-MV triangulation.

Table 1. Accuracy and precision measurements over all fractions and patients comparing KIM with kV-MV triangulation.

Metric	**A-P (mm)**	**S-I (mm)**	**L-R (mm)**
Accuracy (mean)	0.10	0.13	-0.26
Precision (standard deviation)	0.52	0.39	0.52
5^{th} percentile	-0.72	-0.37	-0.69
95^{th} percentile	0.92	-0.61	0.89

Abbreviations: A-P anterior-posterior; S-I superior-inferior; L-R left-right.

Figure 1a

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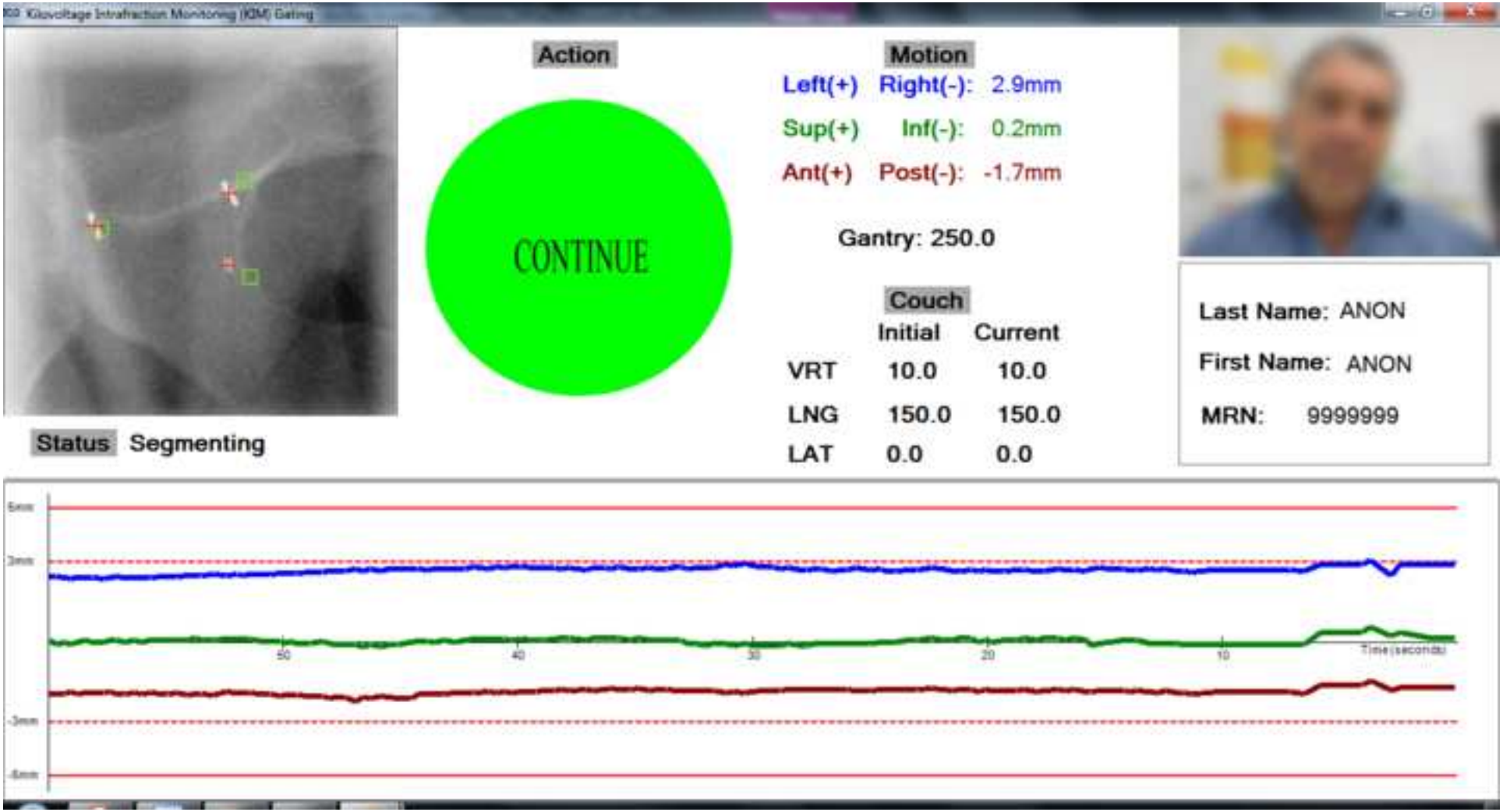

Figure 1b

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Figure 2

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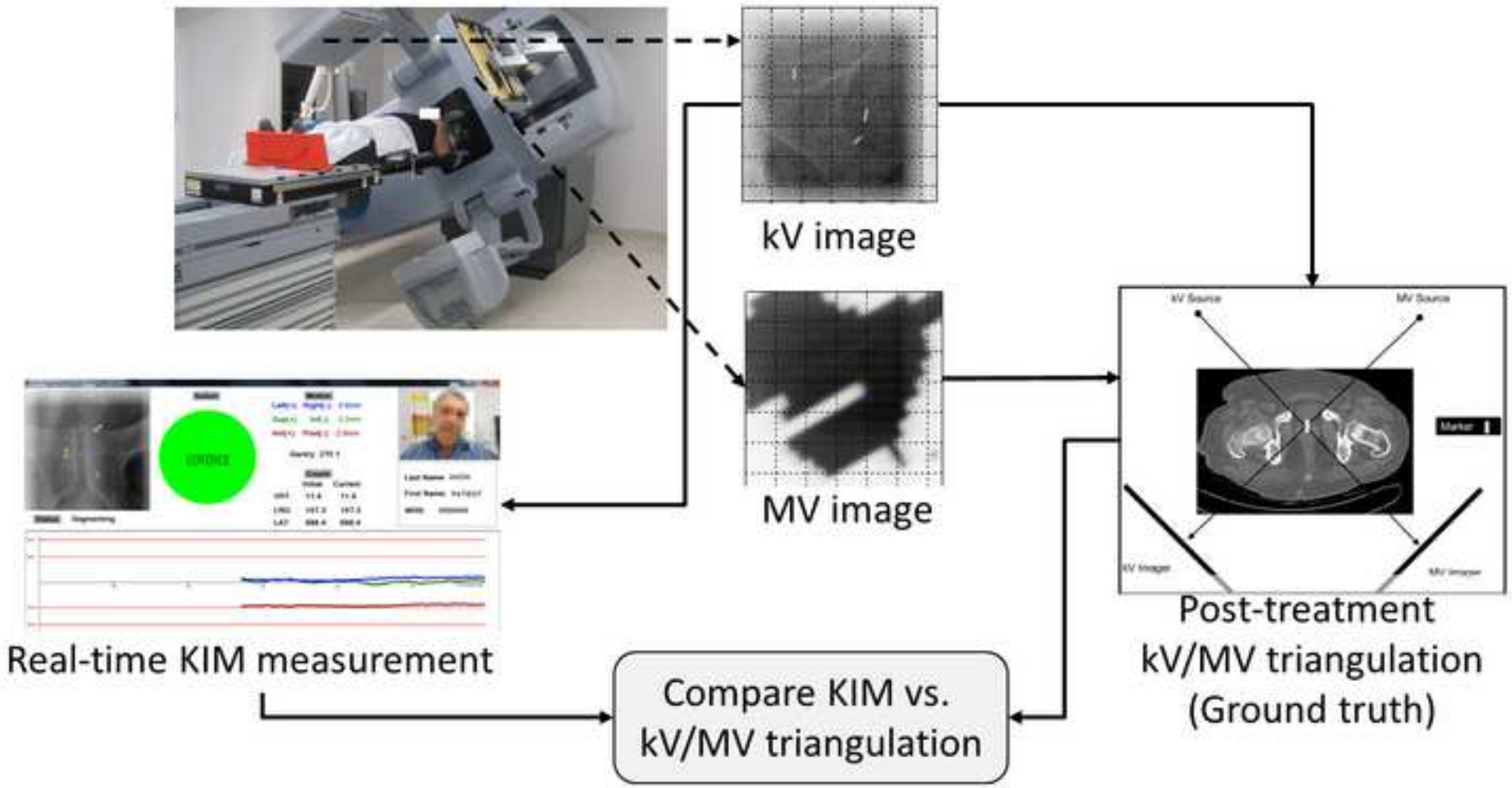

Figure 3a

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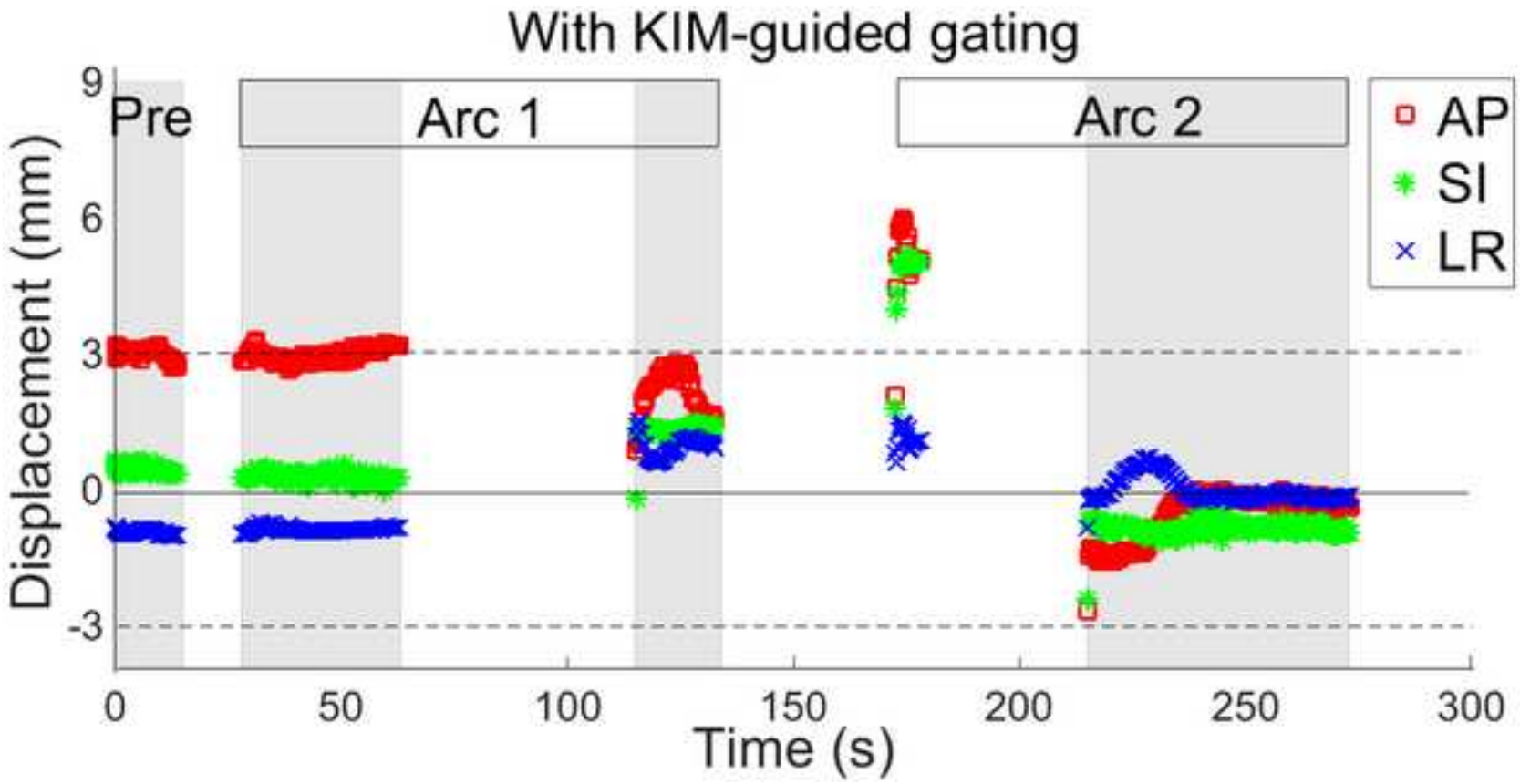

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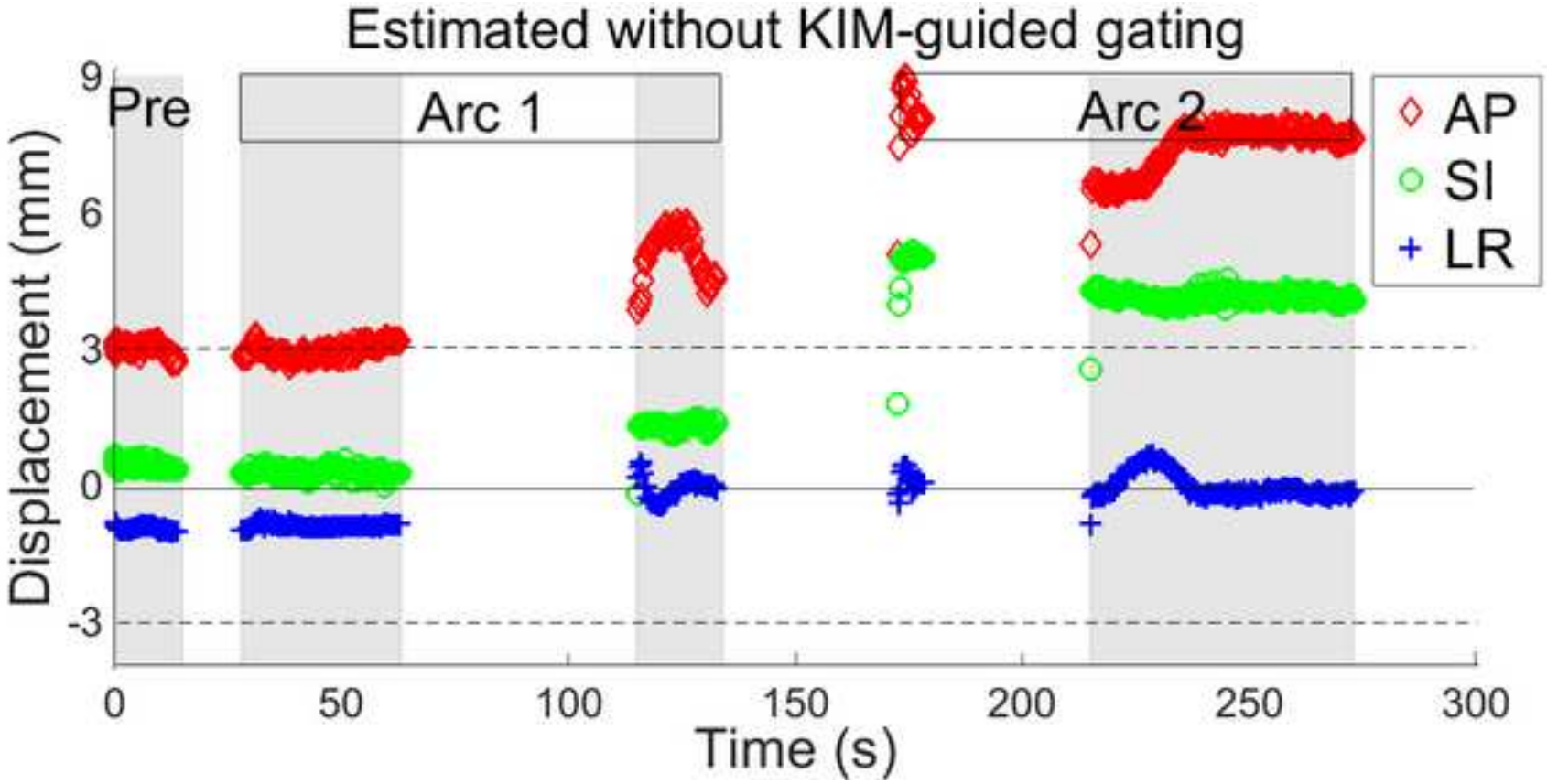

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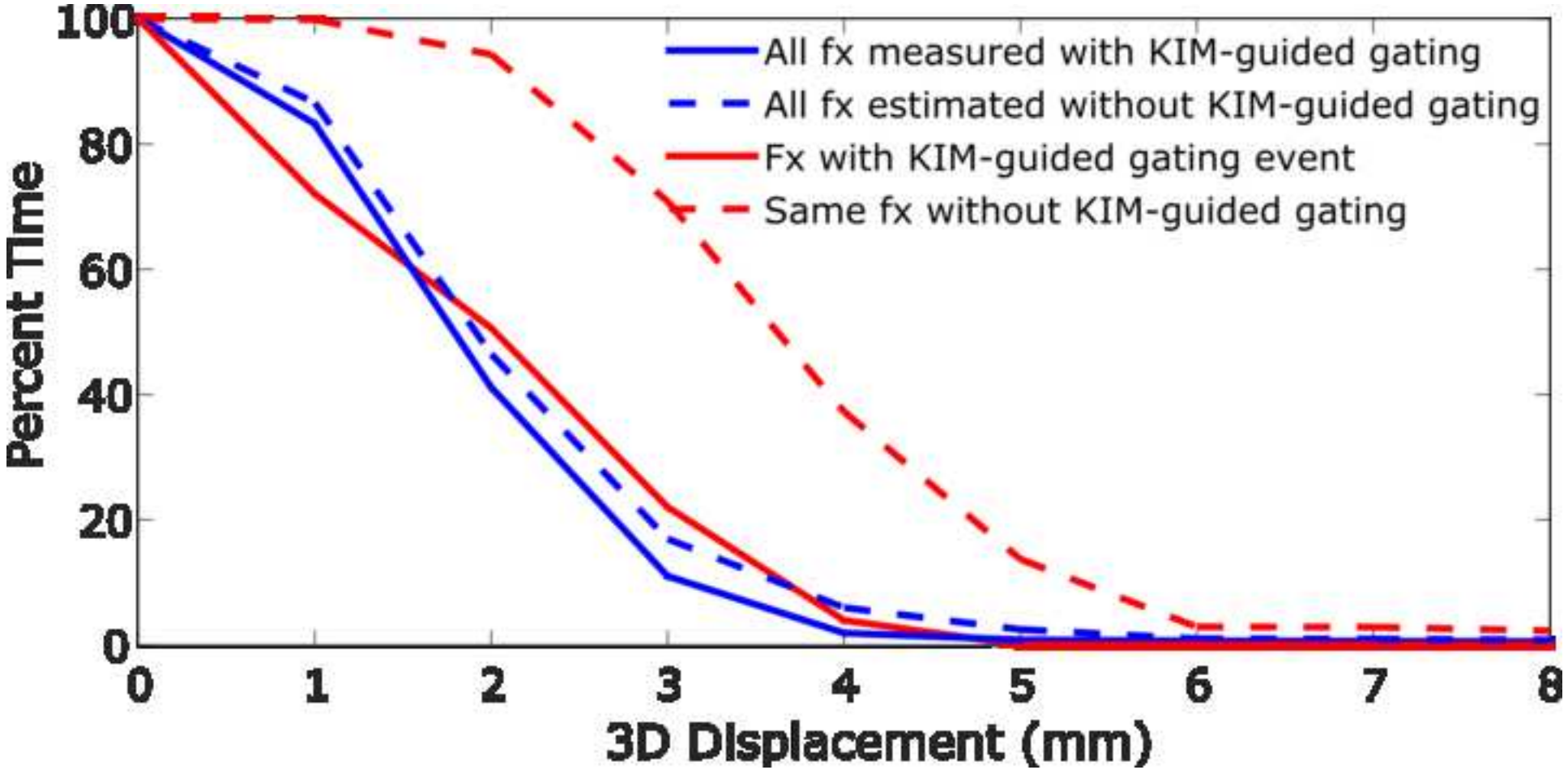

Figure 5

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