Original Research Article

Analysis of intra-fraction prostate motion and derivation of duration-dependent margins for radiotherapy using real-time 4D ultrasound

Eric Pei Ping Pang[a,b,*], Kellie Knight[b], Qiao Fan[d], Sheena Xue Fei Tan[a], Khong Wei Ang[a], Zubin Master[a], Wing-Ho Mui[e], Ronnie Wing-Kin Leung[e], Marilyn Baird[b], Jeffrey Kit Loong Tuan[a,c]

[a] *Division of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610, Singapore*
[b] *Faculty of Medicine, Nursing and Health Sciences, Department of Medical Imaging & Radiation Sciences, Monash University, Wellington Road, Clayton, VIC 3800, Australia*
[c] *Duke-NUS Graduate Medical School, 8 College Road, Singapore 169857, Singapore*
[d] *Centre for Quantitative Medicine, Duke-NUS Medical School, 8 College Road, Singapore 169857, Singapore*
[e] *Tuen Mun Hospital, 23 Tsing Chung Koon Road, Tuen Mun, New Territories, Hong Kong*

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ABSTRACT

Background and purpose: During radiotherapy, prostate motion changes over time. Quantifying and accounting for this motion is essential. This study aimed to assess intra-fraction prostate motion and derive duration-dependent planning margins for two treatment techniques.

Material and methods: A four-dimension (4D) transperineal ultrasound Clarity® system was used to track prostate motion. We analysed 1913 fractions from 60 patients undergoing volumetric-modulated arc therapy (VMAT) to the prostate. The mean VMAT treatment duration was 3.4 min. Extended monitoring was conducted weekly to simulate motion during intensity-modulated radiation therapy (IMRT) treatment (an additional seven minutes). A motion-time trend analysis was conducted and the mean intra-fraction motion between VMAT and IMRT treatments compared. Duration-dependent margins were calculated and anisotropic margins for VMAT and IMRT treatments were derived.

Results: There were statistically significant differences in the mean intra-fraction motion between VMAT and the simulated IMRT duration in the inferior (0.1 mm versus 0.3 mm) and posterior (−0.2 versus −0.4 mm) directions respectively (p ≪ 0.01). An intra-fraction motion trend inferiorly and posteriorly was observed. The recommended minimum anisotropic margins are 1.7 mm/2.7 mm (superior/inferior); 0.8 mm (left/right), 1.7 mm/2.9 mm (anterior/posterior) for VMAT treatments and 2.9 mm/4.3 mm (superior/inferior), 1.5 mm (left/right), 2.8 mm/4.8 mm (anterior/posterior) for IMRT treatments. Smaller anisotropic margins were required for VMAT compared to IMRT (differences ranging from 1.2 to 1.6 mm superiorly/inferiorly, 0.7 mm laterally and 1.1–1.9 mm anteriorly/posteriorly).

Conclusions: VMAT treatment is preferred over IMRT as prostate motion increases with time. Larger margins should be employed in the inferior and posterior directions for both treatment durations. Duration-dependent margins should be applied in the presence of prolonged imaging and verification time.

1. Introduction

Intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) for the treatment of prostate cancer are widely practiced. Both techniques achieve a highly conformal dose distribution, enabling the sparing of surrounding normal tissues whilst delivering the high therapeutic doses. Several papers [1–3] have reported shorter VMAT treatment times compared to routine seven-or nine-field IMRT.

Image guidance allows setup position verification, improves treatment delivery accuracy and eliminates gross errors. With appropriate image guidance, the risk of adverse side effects to organ-at-risk (OARs) can be reduced [4]. Pre-treatment cone-beam computed tomography (CBCT) to correct for setup errors is common, however this only provides a snapshot of the prostate position during the scan and does not provide real-time intra-fraction monitoring of the prostate during the image verification and treatment phases. Intra-fraction motion has previously been rudimentarily calculated based on pre- and post- CBCT

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image registrations [5–8]. More recently there has been a paradigm shift towards the yield of real-time motion data using non-ionizing radiation modalities such as electromagnetic transponders (EMT) and four-dimension (4D) transperineal ultrasound (TPUS).

Numerous studies [9–17] have reported the magnitude and trend of intra-fraction prostate motion using EMT. EMT monitoring is limited to acquiring geometrical coordinates of the transponders and lacks information on soft tissue boundaries of the prostate and surrounding OARs. There are also a limited number of small studies [18,19] (n = 6–10) utilising auto-scanning TPUS for monitoring of intra-fraction motion. The fundamental tracking algorithm of the TPUS system is intensity-based using normalised cross-relation as the cost-function that accounts for surrounding pixels within a 2 mm boundary from the prostate contour [20]. Tracking accuracy of TPUS and EMT has been shown to be comparable within sub-millimetre [13,20–22]. Abramowitz et al. [23] reported agreement of < 0.6 mm maximum distance variation in motion tracking between TPUS and EMT. These previous TPUS studies employed small sample sizes and did not compare margins derived between VMAT and IMRT using patients as their own control.

This study aimed to assess and compare intra-fraction prostate motion between VMAT and IMRT by conducting a motion-time analysis. The study hypothesized that there was a difference in the mean paired prostate motion between VMAT and IMRT in each direction. Duration-dependent planning margins were subsequently derived for both techniques. To our knowledge, this is the first paper to assess differences in observed intra-fraction motion of the prostate using paired TPUS motion data, and the first on an Asian cohort.

2. Material and methods

Ethics approval was obtained in November 2014 and the study registered on the National Institute of Health (NIH) clinical trial registry (ID: NCT02408497). We prospectively recruited 60 consecutive patients from the radiotherapy departments at the National Cancer Centre Singapore (NCCS) and Tuen Mun Hospital, Hong Kong (TMH). All patients (55 from NCCS and 5 from TMH) provided informed consent and received standard VMAT treatment. Patient characteristics are summarised in Table S1 (in supplementary material).

2.1. Patient setup and positioning

Patients were positioned using a knee rest with legs slightly spread (Fig. S1 in supplementary material). Patients followed an individual bladder preparation of 2–3 cups of water (400–600 ml) 30 min before treatment. No specific dietary advice or rectal emptying instructions were given, but patients were encouraged to empty their bowels prior to each fraction. The total imaging and beam-on time required to deliver the prescribed treatment was recorded and the Clarity® system positioning graph was documented for offline analysis against the planning margin employed (Fig. S2 in supplementary material).

2.2. Workflow of 4D TPUS Clarity® system

Before using the 4D Clarity® TPUS system, an infrared-red optical camera was calibrated against the calibration phantom to ensure accuracy of the tracking process during treatment. Due to limited resources, only one 4D Clarity® ultrasound system was located inside our IGRT dedicated treatment room. An autoscan probe (2D frame mode) was held in place for a continuous sweep to acquire a 3D reconstructed dataset [20]. The patient setup workflow process has previously been described [24]. On the first fraction, a routine pre-treatment CBCT was acquired and the patient's position corrected. A reference TPUS scan was then acquired to capture the imaging and treatment position of the prostate. These TPUS images were transferred to a standalone Automatic Fusion and Contouring (AFC) workstation and registered with the

planning CT images [24]. The prostate was contoured offline and used to define the reference positioning volume (RPV) (i.e. prostate gland).

For subsequent fractions, once patients were set up in the treatment position, the ultrasound probe was positioned with reference to the initial probe position to acquire a pre-treatment ultrasound scan. The time taken for the daily imaging regime prior to commencement of treatment was recorded, together with the observed real-time intra-fraction prostate motion.

To simulate prostate motion during an IMRT technique, once weekly all patients remained in the treatment position for an additional seven minutes. This additional seven minutes was based on a retrospective review conducted in our department to determine the average treatment time for VMAT vs IMRT prostate treatments from January to December 2013 (n = 105). This extended tracking time enabled a comparison of intra-fraction prostate motion between VMAT and the simulated IMRT duration for each patient.

2.3. Image verification and treatment time

Daily pre-treatment CBCT was used to verify and correct patient position prior to treatment delivery in this study. Image registration was performed using the integrated algorithm on the Varian on-board imager (OBI) console. Automatic registration using the bony anatomy was performed first, followed by manual fine-tuning to match the primary prostate ± SV volumes. If the difference between the bony and soft tissues registration was within 5 mm, the resultant shift was applied, otherwise the patient was repositioned and re-verified. A total of 1744 treatment fractions from 55 patients demonstrated the mean imaging (4.2 min) and VMAT times (3.4 min) required for prostate radiotherapy (Table S2 in supplementary material).

2.4. Real-time intra-fraction monitoring

Intra-fraction monitoring was continuous and divided into two sequential phases: the imaging and verification phase, followed by the treatment delivery phase. Motion was observed in real-time at a frame rate of 3–4 data points per second depending on the depth and scan angle for each patient. The imaging and verification phase was defined from the time the radiation therapists left the treatment room until the time couch corrections (after CBCT acquisition and assessment) were applied. The treatment phase was defined from the time the couch position application was applied until the beam-off time. For the comparison between VMAT and IMRT treatments, motion data was normalised at the beginning of the treatment phase (i.e. the image frame at that time point was used as the reference position). However, when calculating intra-fraction margins specific to motion detected during the entire imaging and treatment process, motion data was normalised from the start of the imaging and verification phase, thus allowing the true motion related to imaging and treatment duration to be calculated.

2.5. Motion-time trend analysis

Intra-fraction motion was analysed for 55 patients (the imaging phase of TMH patients (n = 5) was not recorded). The entire duration, including the imaging phase, was analysed to elicit the tendency of motion with a temporal resolution of 30 s for an eight-minute period (i.e. the length of a VMAT treatment). A motion-time trend analysis from 1744 monitoring sessions generated a boxplot series (each representing a 30-s period) that illustrated the trend of observed motion for the cohort (n = 55) (Figs. S3–S5 in supplementary material).

2.6. Statistical analysis

A paired *t*-test was used to compare the magnitude of intra-fraction motion between matched IMRT and VMAT sessions (n = 60). The