Inter-fraction prostate motion during intensity-modulated radiotherapy for prostate cancer

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ABSTRACT

Introduction: This study aimed to analyse the inter-fraction prostate motion and setup error during intensity-modulated radiotherapy for prostate cancer at the National Cancer Centre Singapore.

Methods: Gold seeds were implanted as fiducial markers. Daily portal films were taken and displacements of the gold seeds from the isocentre in each axis were recorded. Random and systematic errors were used to derive a margin recipe for each axis based on the van Herk formula.

Results: 1,077 fractions from 36 patients were analysed. 89.8 percent, 85.2 percent and 83.6 percent of the setup errors were within +/− 2 mm for the right-left (RL), superior-inferior (SI) and anterior-posterior (AP) axes, respectively. The population systematic errors were 0.71 mm, 0.84 mm and 0.87 mm; the population random errors were 1.32 mm, 1.59 mm and 1.70 mm; the overall population mean setup errors were −0.14 (range −2.27 to 1.15) mm, 0.11 (range −2.32 to 1.69) mm and 0.08 (range −1.33 to 1.46) mm; and the van Herk margin recipes were 2.69 mm, 3.22 mm and 3.37 mm for the RL, SI and AP axes, respectively.

Conclusion: The setup errors and inter-fraction prostate movements were small. Gold seed implantation is a feasible and easy method of verifying the prostate position.

Keywords: fiducial markers, intensity-modulated radiotherapy, inter-fraction motion, prostate cancer

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INTRODUCTION

With rising awareness and an aging population, an increasing number of cases of prostate cancer have been diagnosed in Singapore.[1] Prostate cancer is usually treated with surgery or external beam radiotherapy; the latter is frequently chosen, as it is non-invasive and more appropriate in patients with intermediate-to-high-risk cancer. Radiotherapy is delivered as small daily doses (fractions) over a period of about seven weeks. Studies have shown that the escalation of radiation dose is associated with improved control rates,[2] and it is now routine to treat the prostate to a total dose of 74 Gy or higher.

At the National Cancer Centre Singapore, prostate cancer is treated with either 3D conformal radiotherapy or since 2004, with intensity-modulated radiotherapy (IMRT). IMRT is a system that allows a high dose of radiation to be delivered to the target volume, which is usually the whole prostate (and part of the seminal vesicles) with a margin around it while minimising radiation to the surrounding normal structures. Over a typical treatment course, the patient is placed in the same position everyday and the same target volume is irradiated. The margin around the prostate is added to compensate for small variations in the daily positioning of the patient (setup errors). However, it is well known that the position of the prostate varies with changes in the bladder and rectal volume as well, regardless of how a patient is positioned.[3] In fact, variations of the prostate position due to internal prostate motion may be more significant than those due to setup errors.[4] Hence, it is important to have a system in place to monitor and correct for any internal movements of the target volume.

Various methods such as gold seeds, transabdominal ultrasonography, computed tomography (CT)-on-rails and radiofrequency transponders have been described in the literature.[5] Gold seeds are radio-opaque fiducial markers implanted within the prostate so that the position of the prostate may be determined with plain radiography. The position of the gold seeds, and thus the prostate, may be checked daily before treatment with an electronic portal imaging device (EPID). Necessary shifts can then be made to the position of the patient to ensure that the target volume remains within the field of treatment. Studies have shown that the implanted gold seeds rarely move inside the prostate.[6] We have

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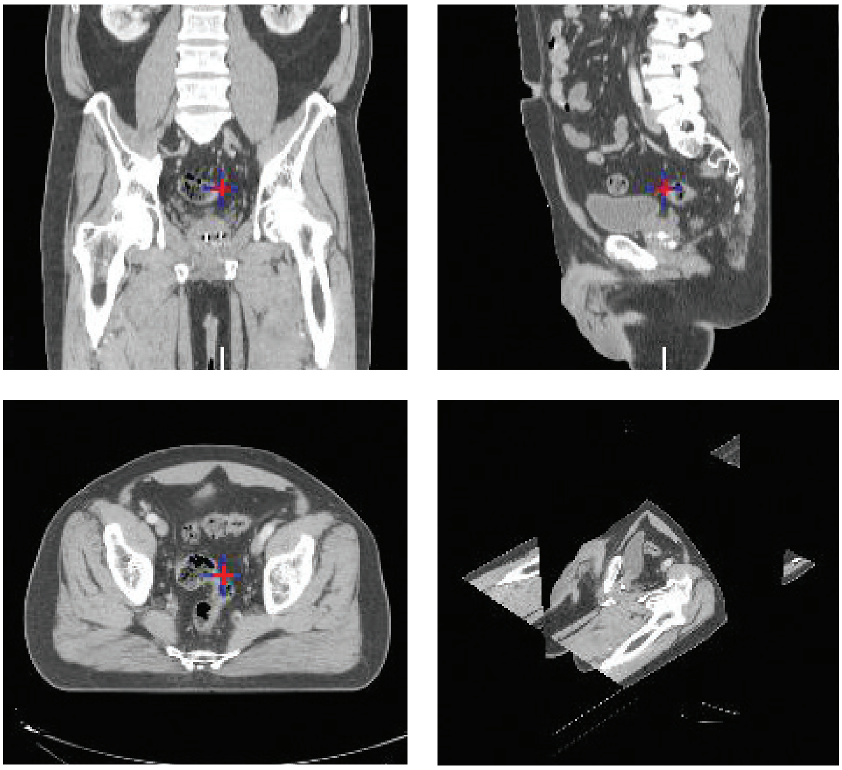

Fig. 1 Simulation CT images for radiotherapy planning.

used gold seeds routinely since mid-2006 and report our experience here.

METHODS

The records of all patients who received IMRT for prostate cancer from 2006 to 2008 were reviewed. For the sake of uniformity, only patients undergoing single-phase radical IMRT to the prostate (for low-to-intermediate risk cancer) were included in the analysis. Patients who did not have gold seeds implanted were also excluded. Three gold seeds, each measuring 3 mm in size, were implanted in the prostate under transrectal ultrasonography guidance by the attending urologist. An ultrasonography probe was used to visualise the prostate, and the seeds were inserted with a needle in the apex and the right and left lobes of the prostate. This is usually a day procedure, and side effects like bleeding and infection are uncommon. Rarely, gold seeds have also been misplaced in the mesorectal fascia or bladder wall with no untoward complications.

Gold seeds were implanted in all patients who were planned for IMRT as far as possible. About one week after implantation, simulation or planning CT imaging was performed for each patient in the supine position, with the lower limbs supported with a limb immobilisation device. This CT image was used to delineate the target volume and for treatment planning (Fig. 1). Once planning was completed, a pair of digitally reconstructed radiographs (DRRs) was generated for the anterior and lateral views of the pelvis. Unlike the prostate, the radio-opaque gold seeds were readily identifiable on the DRRs (Fig. 2) and acted as surrogate markers for the position of the prostate. Patients were simulated and treated with an empty bladder. Some centres routinely treat the prostate with a 'comfortably full' bladder to displace the small bowel cranially and thus, minimise the dose to the organ at risk. However, short of catheterising a patient, it is difficult to accurately reproduce the bladder volume everyday, leading to potential variations in the position of the prostate. As an empty bladder is more reproducible, the IMRT technique was used to limit the dose to the small bowel within the treatment fields. Besides dietary advice, no other measures were taken to control the volume of the rectum or bladder. The dose prescribed was 70–74 Gy to the prostate, at 2 Gy per fraction over 7–7.5 weeks.

Patients were positioned according to their skin markings and tattoos. Prior to treatment, a pair of orthogonal portal films or radiographs (Fig. 3) was taken with EPID (everyday for most patients). The position of the gold seeds on the portal films was then compared with that on the DRRs derived from the planning CT to verify the position of the isocentre or the centre of the target volume. With the help of the treatment software, displacements of the isocentre were then measured with respect to the gold seeds. The patient was then shifted accordingly in the superior-inferior (SI), right-left (RL) and anterior-posterior (AP) directions to correct for

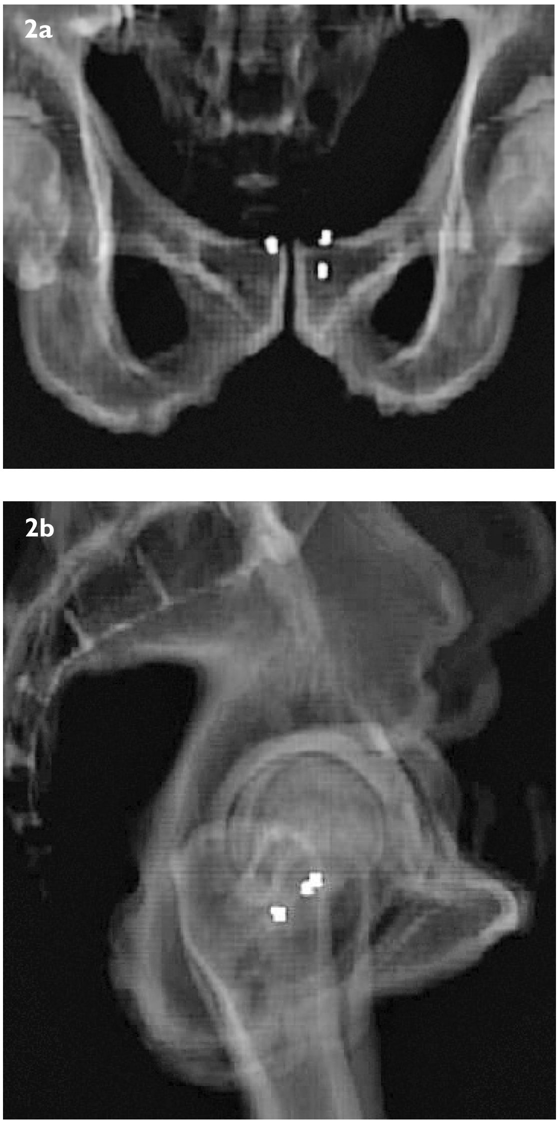

Fig. 2 Digitally reconstructed radiographs generated from the simulation CT show (a) the anterior-posterior view and (b) the lateral view.

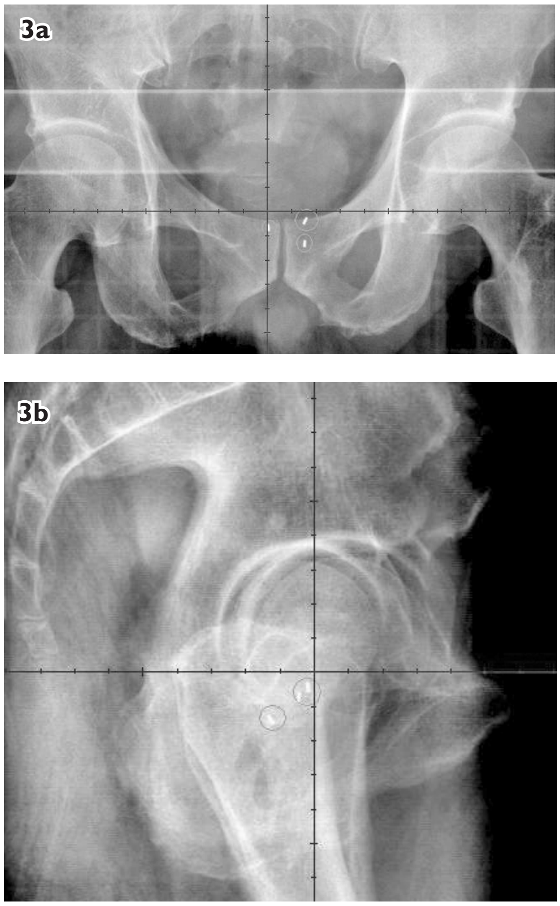

Fig. 3 Portal film radiographs show (a) the anterior-posterior view and (b) the lateral view.

these differences, thus bringing the planned treatment volume back to the same position as it was on the day of the simulation CT imaging. This ensures that the whole treatment volume receives the planned radiation dose and that dose to the neighbouring normal organs is minimised. The anterior film was used for displacements in the SI and RL directions, while the lateral film was used for the AP direction. Correction shifts were made for any displacements > 1 mm. The coordinates of the isocentre were not changed for subsequent treatments, and daily shifts were made with respect to the original (planning) isocentric position.

The individual and population systematic and random setup errors were calculated. As correction shifts were based purely on the differences between the planning isocentre and the position of the gold seeds, the setup error in this instance reflects both positioning uncertainties as well as inter-fraction prostate motion. These figures were calculated for each axis (AP, SI and RL) and applied to the margin recipe described by van Herk[7] in order to derive the individual margin for the planning target volume (PTV) for each axis. The recipe is given by: $2.5\Sigma + 0.7\sigma - 3$ mm, where Σ is the standard deviation (SD) of systematic errors and σ is the SD of random errors. Σ is derived by calculating the SD of the mean of the daily measurements of each patient, while σ is derived from calculating the root mean square of the SD of the daily measurements of each patient. The use of this recipe is meant to guarantee that 90% of patients in the population receive a minimum cumulative clinical target volume (CTV) dose of at least 95% of the prescribed dose.

RESULTS

A total of 157 patients with prostate cancer were treated with IMRT from June 2006 to October 2008. Of these, 36 patients fulfilled the inclusion criteria for our analysis. 20 of these patients had daily portal films and shifts, while 78% had at least 25. This added up to a total of 1,077

Table I. Number and total magnitude of shifts in each direction.

	Right	Left	Superior	Inferior	Anterior	Posterior
No.	249	317	353	267	322	301
Magnitude (mm)	421	599	705	520	720	594

fractions. The mean setup errors for the RL, SI and AP axes were 12 (range 5 to –7) mm, 21 (range 9 to –12) mm and 20 (range 10 to –10) mm, respectively. There were more shifts in the left, superior and anterior directions. The predominant motions in terms of overall magnitude were in the superior and anterior directions (Table I). Half of the patients had individual setup error ranges that were > 5 mm in at least two axes. However, 89.8%, 85.2% and 83.6% of the setup errors were within 2 mm and –2 mm for each direction, and no shifts were necessary in 47.0%, 41.5% and 42.1% of the 1,077 fractions, respectively. The frequency distribution of the prostate movement in the RL, SI and AP directions is shown in Fig. 4.

The population systematic errors for the RL, SI and AP axes were 0.71 mm, 0.84 mm and 0.87 mm, respectively. The population random errors were 1.32 mm, 1.59 mm and 1.70 mm, respectively, while the overall population mean setup errors were –0.14 mm (–2.27 to 1.15), 0.11 mm (–2.32 to 1.69) and 0.08 mm (–1.33 to 1.46). Applying the van Herk formula, the margin recipes for the RL, SI and AP axes were 2.69 mm, 3.22 mm and 3.37 mm, respectively.

DISCUSSION

The use of implanted fiducial markers to assess and monitor prostate motion is not new, and its feasibility was demonstrated as early as 1995.[8-10] With the positive results of dose escalation trials,[2] it has become increasingly common to treat the prostate to 74 Gy and more. However, the safe delivery of such doses requires greater precision in dose delivery so as to minimise toxicity to the organs at risk. This is usually achieved by reducing the PTV margin, and hence the overall radiation treatment volume, using various methods. A simple and readily implemented way is the use of gold seeds implanted in the prostate. By monitoring the position of the gold seeds on EPID during the course of treatment, corrections can be made for any changes in the isocentric position. The PTV margin can then be safely reduced, without compromising efficacy or safety.

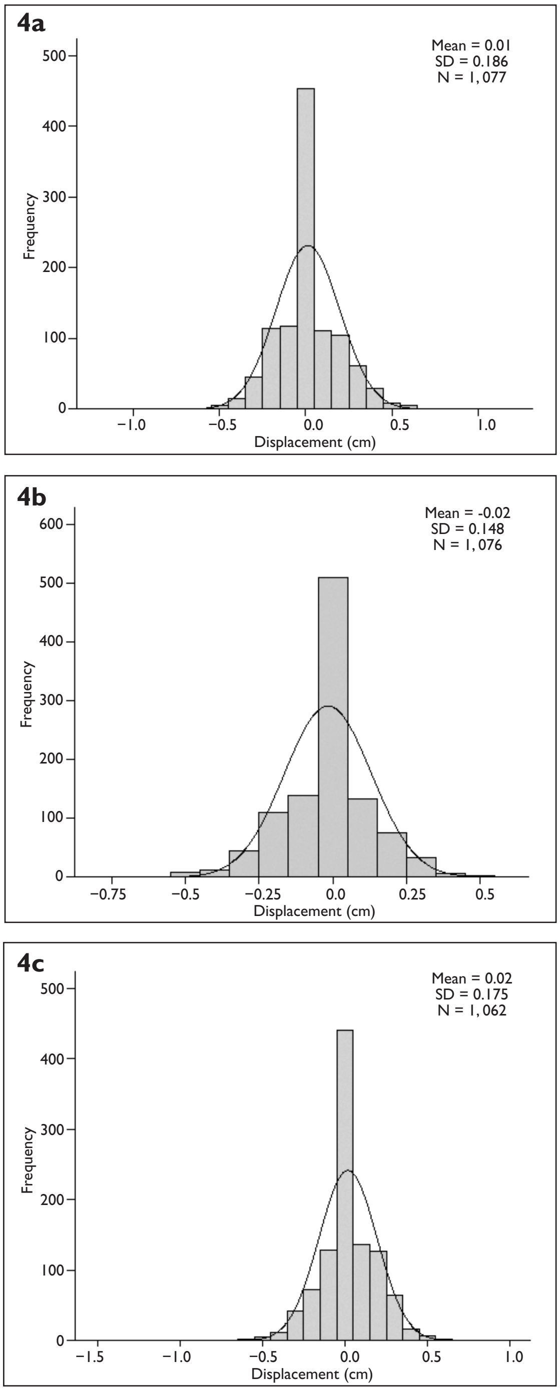

Fig. 4 Graphs show the frequency distribution of prostate motion in the (a) anterior-posterior (AP); (b) right-left (RL); and (c) superior-inferior (SI) directions.

As displacements of the isocentric position reflect both setup errors (or positioning of patient) and inter-fraction prostate movements in our study, we are unable to report the exact magnitude of the latter in our patients during their course of treatment. However, we can conclude that the prostate moves no more than 7 mm, 12 mm and 10 mm in the RL, SI and AP directions, respectively. The margin recipe is thus the margin necessary to apply to the CTV to account for these two uncertainties. Our immobilisation techniques and relatively simple bowel and bladder preparations were sufficient to minimise prostate movement. While extremes of displacement of ≥ 7 mm were recorded in each axis, the SD of these shifts was very narrow and over 80% were ≤ 2 mm. This compares favourably with results from other centres; Wu et al reported prostate motion of ≤ 5 mm in over 90% of observed movements (based on 272 portal images from 13 patients),[11] while Vigneault et al reported movements of ≥ 5 mm in about 17% of movements in the AP as well as SI directions (based on 900 portal images from 11 patients).[12]

In a large study conducted recently, Osei et al analysed 4,878 portal images from 118 patients, and reported displacements of ≤ 3 mm in the RL, SI and AP directions in 83.6%, 70% and 49% of movements, respectively.[13] The large displacements in the AP direction may be related to the fact that the patients in their study were treated with a full bladder everyday (as opposed to the empty-bladder protocol used in our study). Inconsistent daily bladder filling may have contributed to the larger variations in the AP displacements.

Our study is limited by the inconsistent quality of the portal images (treatment machine-dependent) and possible interobserver variability in the manual measurement of the gold seed displacements. In addition, portal images were not taken after each fraction and no attempt was made to measure any possible intra-fraction prostate movement. However, in their study of ten patients during 251 radiotherapy fractions, Nederveen et al reported that on average, the intra-fraction prostate motions did not result in margins > 1 mm.[14] The margin recipe derived from the van Herk formula should serve only as a guide to the attending radiation oncologist when deriving the PTV margin during planning.

In conclusion, the setup errors and inter-fraction movements of the prostate were small in our study population. We have demonstrated that our combination of immobilisation, empty-bladder protocol and bowel advice was sufficient to minimise displacements in the isocentric position. Gold seed implantation is also a feasible and easy way of verifying the prostate position during the course of radiotherapy.

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