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Assessment of motion and field placement verification of the prostate using gold seed fiducial markers: a feasibility study

AL Brown and EL Day

Townsville Cancer Centre, The Townsville Hospital, Townsville, Queensland 4814, Australia.
Correspondence amy_brown@health.qld.gov.au

Abstract *Purpose:* The aim of this study was to determine the feasibility of using gold seed fiducial markers within the daily treatment of prostate cancer patients as a means of improving treatment field placement accuracy and minimising the effect of interfractional prostate movement. *Methods:* Ten patients had three fiducial markers inserted into the prostate gland under ultrasound guidance. Daily verification images were acquired throughout standard radiation therapy treatment with the measurement, comparison and analysis of bony anatomy displacement to fiducial marker displacement performed. *Results:* Greater than 20% of measurements in the superior/inferior (SI), anterior/posterior (AP) directions and displacement magnitude, would have resulted in a different action when using bony anatomy compared to fiducial markers, compared to less than 3% in the right/left (RL) direction. The mean prostate displacement was 0.46, 1.52 and 1.75 mm in the LR, SI, and AP directions respectively. The maximum prostate displacement was 10, 16 and 18 mm in the LR, SI, and AP directions respectively. Mean displacement magnitude was 6.32 mm, with a maximum displacement magnitude of 18 mm. *Conclusion:* This trial supports the growing body of evidence that there is benefit in the use of daily imaging with prostatic gold seed fiducial markers for more accurate treatment localisation.

Keywords: fiducial markers, prostate localisation, prostate movement.

Table 1: Inclusion and exclusion criteria for patient participation.

Inclusion	Exclusion
Patients with histologically confirmed adenocarcinoma of the prostate.	Evidence of distant metastases.
	Lymph node involvement, either clinically, radiologically, or pathologically.
	Previous or concurrent cancers other than non-melanomatous skin cancer.
Patients must sign an informed consent prior to being placed in the study.	Major intercurrent physical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment or adequate follow-up either through disablement or limitation of life expectancy to less than 1 year.
Performance status must be equal to or less than ECOG 1.	Performance status of greater than 1 on the ECOG scale.
Patients who live locally within the immediate area.	Patients who do not live within the immediate area.

Introduction

The prostate is a mobile organ. Studies have shown the significance of both interfractional and intrafractional organ movement in relation to pelvic bony anatomy, particularly of the prostate due to such factors as rectal and bladder filling.[1] Current practice to minimise this motion includes rectal and bladder filling protocols, and patient stabilisation, however, studies report prostate motion of an average of 2–6 mm and maximums of up to 20 mm.[2,3] Such movements are detrimental to the optimal delivery of radiotherapy, resulting in potential under or over-dosing of the planned target volume (PTV), and potential over-dosing of surrounding critical structures, such as bowel and bladder.

Gold seed fiducial markers have been found to be an accurate and efficient method of pre-treatment prostate localisation by previous studies.[1–8] O'Daniel, *et al*.[4] compared several target alignment methods including skin mark alignment and bony registration, daily ultrasound and daily computed tomography (CT) scan. It was found that relying on skin marks and bony registration resulted in an adequate PTV coverage in just 70% of patients.[4] In addition to the dosimetric coverage, other factors such as machine and equipment requirements and cost; alignment technique time, complexity and invasiveness; and staff expertise and training should be considered.[2]

The aim of the study is to determine the feasibility of using gold seed fiducial markers for daily localisation of the prostate as a means of improving treatment accuracy, and minimising the effect of interfractional prostate movement. In doing so, the study also aimed to quantify the movement of the prostate during a radiation therapy treatment course, accurately assess the treatment field placement in relation to the prostate itself rather than the traditional relationship of field placement matched to pelvic bony anatomy, and to assess inter-user variability in point registration matching of the gold seed fiducial markers.

Methods

Ethics approval through the District Ethics Committee was

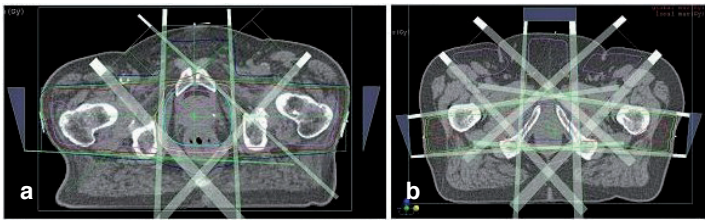

Figure 1: Treatment beam arrangement, with either (a) direct laterals or (b) posterior oblique beams.

sought and granted prior to recruitment of patients. Ten patients were selected as per selection criteria (Table 1), and consented by the radiation oncologist. The trial was limited to prostate patients living within the immediate area defined as within a 100 km radius from the treatment centre, so as not to unnecessarily inconvenience patients from the greater service area.

Between March and April 2008, each patient was implanted with three ACCULOC® (Civco Medical Solutions, Iowa, USA) fiducial markers. The fiducial markers were implanted into the base, apex and lateral mid-gland of the prostate under the guidance of a trans rectal ultrasound (TRUS) by an urologist under local anaesthetic, and prescribed prophylactic antibiotics. Implantation occurred at least one week prior to the planning CT scan to allow oedema to subside. The ACCULOC® markers were 3 mm x 1 mm cylindrical, 99% pure gold markers, with a cross-hatched surface to minimise migration. A self-assessed survey was conducted to evaluate how the patient perceived their comfort levels during implantation. Patients rated the discomfort associated with their implantation procedure on a scale of 1 to 10, with 1 being comfortable and 10 being very uncomfortable (Fig. 2).

Patient CT simulation and planning occurred as per departmental protocol. Patients were positioned supine with a Combifix™ (Civco Medical Solutions, Iowa, USA) fixed knee and ankle position. Three tattoos, one each on the anterior and lateral aspects of the bony pelvis were given as permanent set-up skin marks. Departmental protocol of empty rectum with Fybogel™ (Reckitt Benckiser Pty Ltd, Slough, UK) taken in the week prior to simulation, and throughout treatment; and full bladder (2 x 300 mL glasses of water, 20 minutes prior to CT simulation and daily treatment) was adhered to. Treatment staff verbally checked with the patient that they had emptied their bowels and drunk the required water before bringing the patient into the treatment room. A pelvic CT of 3 mm slices was obtained, with digital reconstructed radiograph images (DRRs) generated from this.

All patients were planned on XiO® (CMS Inc, Missouri, USA) radiotherapy planning system using a single phase five field 10 MV beam arrangement as shown in Figure 1. The PTV, rectum, and bladder were contoured by radiation oncologists. The PTV included the prostate and any local tumour extensions, with a margin of 10 mm circumferentially except 7 mm posteriorly. Patients were prescribed 74 Gy in 37 fractions over 7.5 weeks. If dose constraints for the rectum could not be met, a two-phase technique was planned. This occurred for three out of the 10 patients. When a two-phase technique was used, the above PTV was prescribed to 60 Gy in 30 fractions, with a boost of 14 Gy in seven fractions to the prostate only with a margin of 10 mm circumferentially except 7 mm posteriorly.

Patients were treated on an Elekta Precise® (Elekta Ltd, Crawley, UK) linear accelerator as per current departmental protocol, aligning the anterior and lateral tattoos and setting the isocentre relative to the anterior tattoo with a fixed couch height. Weekly isocentre portal verification images acquired and assessed online in relation to bony anatomy. In addition, daily treatment "capture" images of the anterior and most lateral aspects were acquired for assessment offline in relation to fiducial markers and bony anatomy. The final patient completed treatment in mid November 2008.

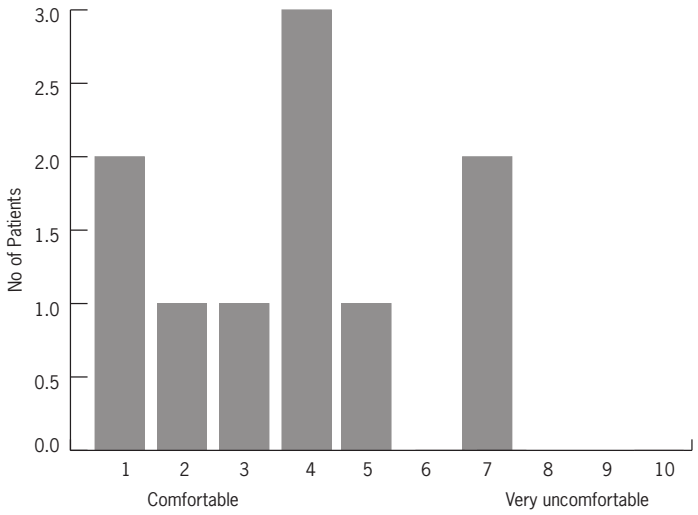

Figure 2: Results of seed implantation comfort rating survey.

Bony displacement was determined by manually registering to the bony anatomy utilising IViewGT™ (Elekta Ltd, Crawley, UK) software. Fiducial marker displacement was determined using the point registration function of ViewStation software in MOSAIQ™ (IMPAC Medical Systems, Inc., California, USA). ViewStation utilised a "point matching algorithm" to find the best fit for all three seeds and calculate the shifts required in the right/left (RL), superior/inferior (SI) and anterior/posterior (AP) directions. Data collation and analysis was performed to evaluate the two different field placement verification methods, with both the registrations and data entry of results being independently verified by a second radiation therapist not directly involved in the study.

Displacement magnitude was calculated using the formula (1):

$$(1)\ \text{Displacement magnitude} = \sqrt{RL_n^2 + AP_n^2 + SI_n^2}$$

Inter-user variability of point registration was quantified by comparing and analysing 10 qualified radiation therapists' recorded displacements for 10 consecutive image pairs.

Statistical analysis was performed using the data analysis package within Excel™.

Results

The average age of patients recruited was 71 (range: 60–79 years) with T1b to T2c staging; presenting PSA ranging from 2 to 18; and a Gleason score between 6 and 7. The mean Body Mass Index (BMI) of patients was 32.4, SD = 7.9; Range = 22.8 to 46.9). Eight out of 10 patients had undergone a transurethral resection of the prostate (TURP) and 7 out of 10 patients underwent neoadjuvant hormone therapy (Eligard Sanofi-aventis NJ, USA and Androcur Schering Berlin, Germany). The mean time between implantation and CT planning scan was 55 days (SD = 48.5; Range: 10–150).

No major acute complication was reported by patients with regards to implantation. Survey results of comfort of the implantation procedure are shown in Figure 2. The median comfort rating was 4 (range = 1 to 7).

Table 2: Agreement and disagreement between fiducial markers vs bony anatomy in left/right, anterior/posterior and superior/inferior directions, and displacement magnitude.

5 mm Tolerance Agreement and Disagreement	**Right/Left count (%)**	**Superior/Inferior count (%)**	**Anterior/Posterior count (%)**	**Displacement Magnitude count (%)**
Fiducial markers **out of** tolerance Bony anatomy **within** tolerance	6 (1.7%)	64 (18.2%)	43 (12.3%)	78 (22.2%)
Fiducial markers **within** tolerance Bony anatomy **out of** tolerance	3 (0.9%)	13 (3.7%)	40 (11.4%)	31 (8.8%)
Total disagree	**9 (2.6%)**	**77 (21.9%)**	**83 (23.6%)**	**109 (31.1%)**
Fiducial markers **out of** tolerance Bony anatomy **out of** tolerance	10 (2.8%)	11 (3.1%)	29 (8.3%)	148 (42.2%)
Fiducial markers within tolerance Bony anatomy within tolerance	332 (94.6%)	263 (74.9%)	239 (68.1%)	94 (26.8%)
Total agree	**342 (97.4%)**	**274 (78.1%)**	**268 (76.4%)**	**242 (68.9%)**
Total	**351 (100%)**	**351 (100%)**	**351 (100%)**	**351 (100%)**

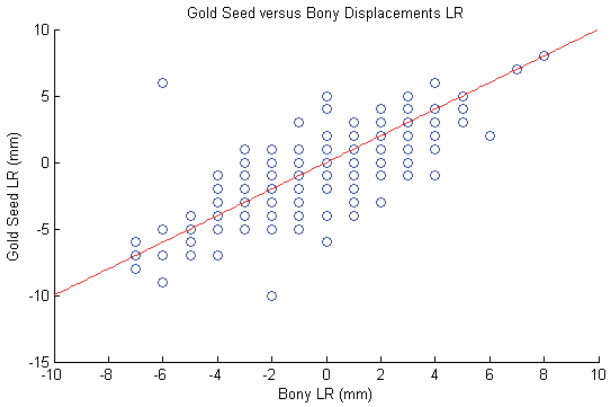

Figure 3a: Correlation graph of displacement in RL direction for fiducial marker and bony methods.

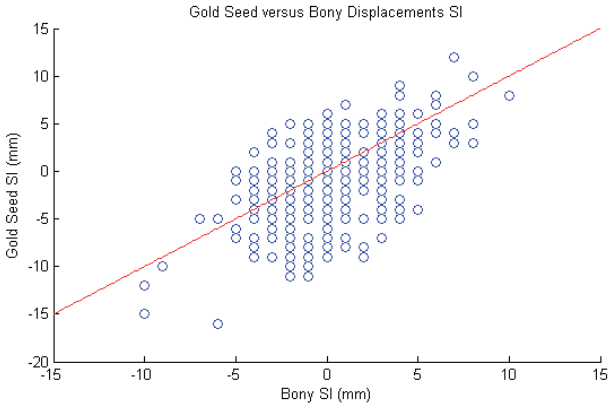

Figure 3b: Correlation graph of displacement in SI direction for fiducial marker and bony methods.

In total, 737 isocentre film captures were acquired out of a total possible 740 (99.6%), comprising 357 anterior aspect film captures and 359 lateral captures. A total of 351 (96.5% of 370 possible) orthogonal pairs were assessed for both bony displacement and marker displacement.

Matching performed utilising the fiducial markers was not always in agreement with bony anatomy matching. Agreement and disagreement between the two techniques using the current departmental tolerance of 5 mm are displayed in Table 2.

Of the images assessed, 37% of fractions measured differed ≥ 5 mm in at least one direction in relation to the fiducial markers. Displacements in the RL, SI and AP greater than 5 mm were 4.8%, 20.5% and 20.3% respectively, with a distance magnitude greater than 5 mm in 64.1% of fractions. Comparatively, when assessed in relation to bony anatomy, 28% of fractions were ≥ 5 mm in at least one direction. Displacements in the RL, SI and AP greater than 5 mm were 3.6%, 6.6% and 19.8% respectively, with a distance magnitude greater than 5 mm in 50.7% of fractions. These marker and bony displacements correlations are shown in Figure 3, with the reference line indicating when both marker and bony displacements were equal.

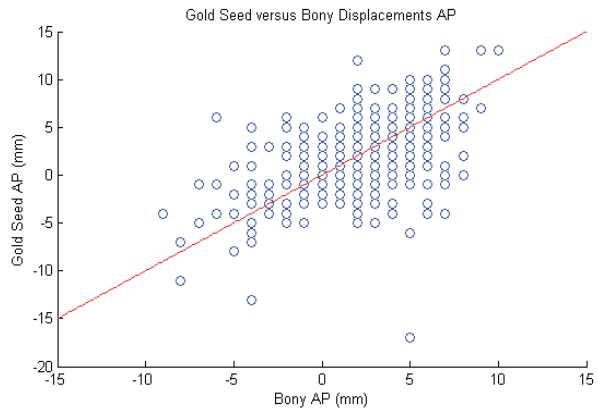

Figure 3c: Correlation graph of displacement in AP direction for fiducial marker and bony methods.

The mean displacement with marker registration in either the

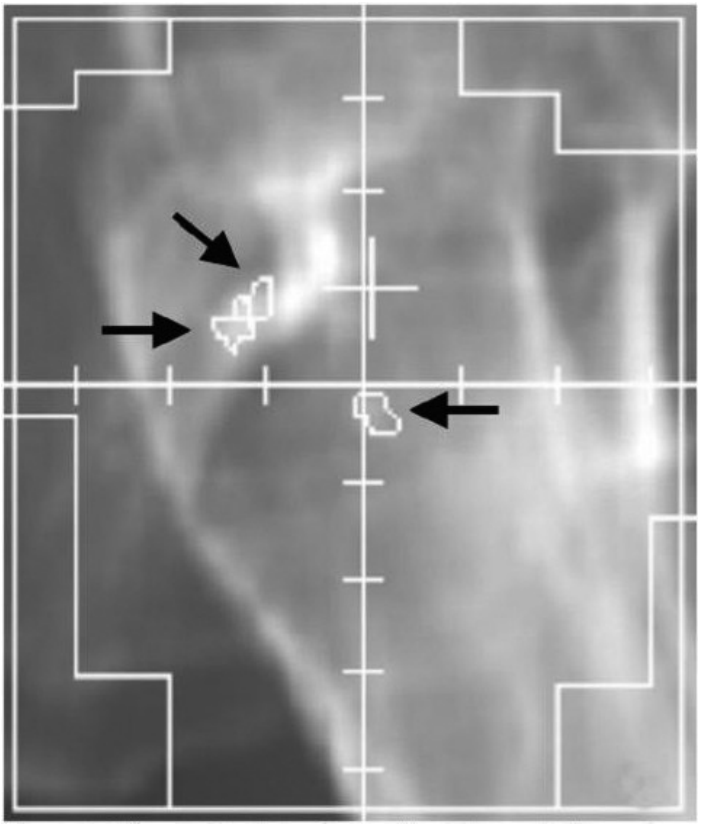

Figure 4: DRR with fiducial markers outlined, demonstrating markers close to overlapping.

left or the right direction was 0.46 mm right (SD = 2.86; 95% CI = 2.68 to 3.10). More deviations were in the right than the left direction (46.2% and 39.6% respectively, with 14.2% of zero displacement). The maximum displacement was 10 mm.

The mean displacement with marker registration in either the superior or inferior direction was 1.52 mm inferior (SD = 4.32; 95% CI 4.07 to 4.6). More deviations were in the inferior than the superior direction (58.4% and 32.1% respectively, with 9.6% of zero displacement). The maximum displacement was 16 mm.

The mean displacement with marker registration in either the anterior or the posterior direction was 1.75 mm anterior (SD = 4.17; 95% CI 3.87 to 4.49). More deviations were in the anterior than the posterior direction (61.3% and 30.1% respectively, with 8.6% of zero displacement). The maximum displacement was 18 mm.

The mean displacement magnitude with marker registration was 6.32 mm (SD = 3.12; 95% CI 2.91 to 3.38). The maximum displacement was 18 mm.

Inter-user variability of the fiducial matching was found to have a maximum difference of 3 mm (range = 0.4 mm to 3 mm), with a mean difference of 1.5 mm (SD = 0.21). The clinical experience of staff completing the inter-user variability test ranged from one to six years, with a mean of three years experience.

Discussion

This study aimed to determine the feasibility of using gold seed fiducial markers as a means of improving accuracy and minimising the effect of interfractional prostate movement. Our study supports the growing body of evidence that the use of fiducial markers has the potential to increase accuracy of treatment.

Study findings and existing evidence

The prostate displacements measured and presented are supported by several previous studies showing the most motion in the superior/inferior and anterior/posterior direction rather than the right/left.[3–6] This is reflected in our findings that 21.9% and 23.6% in the SI and AP directions respectively, would have resulted in a different action when using bony anatomy or fiducial markers, compared to only 2.6% in the RL direction.

This can be accounted for in the variance of daily bladder and rectal filling, and potential varying pelvic tilt within the stabilisation device. As with our results showing more deviations in the anterior than posterior directions (61.3% *v* 30.1%), Chen, *et al*.[7] also report more deviations in the anterior direction (70% *v* 16%), however found more deviations in the superior than inferior (60% *v* 29%), compared to our findings of more in the inferior (58.4% *v* 32.1%). This may be due to differing bladder and bowel preparations, which were not detailed. It should also be noted that their 33 patient cohort was more statistically significant than our sample size. Schallenkamp, *et al*.[5] report prostate displacements of up to 15 mm RL, 16 mm AP and 9 mm SI, with average displacements reported to be 2 mm RL, 4 mm AP and 3 mm SI. This is comparable to our maximums of 10 mm RL and 18 mm AP, but not so for our maximum of 16 mm SI. Dehnad, *et al*.[6] also reported mean displacements of 2.1 mm RL, 3.2 mm AP and 2.2 mm SI. Our mean displacements of 0.46 mm RL, 1.52 mm AP and 1.75 mm SI are comparable to these studies, with greater enforcement of bladder and bowel preparation perhaps contributing to the difference between these.

Departmental prostate correction tolerance is currently 5 mm in any direction, and therefore, matching to fiducial markers online would have necessitated shifts in 38.2% of total fractions, compared to 30.2% of total fractions when matching to bony anatomy. With an action tolerance of 3 mm, Chen, *et al*.[7] reported 90% of all treatments required a shift. Based on our results, should a departmental tolerance of 3 mm be adopted, 69.5% of fractions would have necessitated a shift, matching to fiducial markers.

Inter-user variability and overlapping markers implications

Inter-user variability was investigated for both bony anatomy matching and fiducial marker matching. The inter-user variability for fiducial marker matching of 3 mm maximum was as expected, due to the length of the seed. The 3 mm length of each marker is a limitation in improving this, as the registration point could potentially be placed at any length along this. In order to minimise this, treatment radiation therapist staff are instructed to place the registration point as close as visually possible to the centre of the marker.

Field edge detection, a feature of the ViewStation software (IMPAC Medical Systems, California, USA) to place the isocentre on the portal image is also a source for variability, particularly under time pressures in a clinical online setting, however, this was a part of the inter-user variability test, and therefore is accounted for within the 3 mm maximum.

The radiation therapists undertaking the inter-user variability test were of varied years of experience, with no staff member having previous experience of the point registration function of ViewStation until recent introduction to the department.

A further limitation of this study was the use of two different systems for measurement of bony displacement (IViewGT™, Elekta, Crawley, UK) and fiducial marker displacement (ViewStation software in MOSAQ™, Elekta, Stockholm, Sweden), as IViewGT™ does not accommodate fiducial marker matching, and at the time, MOSAIQ™ could not be used clinically for bony anatomy matching within the department. As the department transitions from IViewG™ to ViewStation software in MOSAIQ™, this can be addressed further.

In observations, two out of 10 patients had the markers implanted in the lateral mid-lobes (as opposed to the apex and

lateral lobe) quite close to overlapping on lateral DRR and portal images, as shown in Figure 4. Overlapping markers could potentially result in an inaccurate shift. The occurrence of this overlapping can be improved through further liaising with and increasing experience of urology staff.

Advantages and disadvantages

Gold seed fiducial markers are considered to have several advantages over other methods, as there is no machine modification required; and pre-treatment assessment is achieved relatively efficiently, adding only minutes to treatment time.[8] The time implication of daily imaging and potential daily shifts is an area for future departmental assessment, given that current imaging protocol is to image on a weekly basis. Automated couch movement from the linac controls could make the process more efficient; however this is currently not available within the department.

Greater accuracy in the treatment of prostate cancer has the potential to lead to reduced margins, which results in decreased toxicity.[9] Studies have shown that by reducing the PTV by 5 mm as a result of the reduction of geometrical errors, rectal toxicity is in turn reduced.[10] However, if daily movement is substantial, reduction of margins results in a geometrical miss.[11] As rectal toxicity is one of the most common side effects of prostate radiation therapy, the possible reduction of rectal complications is an important rationale for the use of gold seed fiducial markers. Skala, *et al*.[12] reports when using fiducial marker correction with intensity modulated radiation therapy (IMRT) to 75.6Gy, the rate of patient-reported ≥ Grade 2 rectal toxicity at median 37 months follow up, was 3.2%, compared to 12% to 26.5% in studies of similar planning techniques and dose regimens. Greater accuracy in the treatment of prostate cancer also has the potential to lead to dose escalation which results in improved local control and increased tumour control probability (TCP), without a significant corresponding increase in toxicity.[13] For intermediate risk prostate patients it has been reported that the use of gold seed fiducial markers in conjunction with dose escalation, resulted in an increased TCP of 60–80%.[10] Nichol, *et al*.[14] report that dose escalation improved biochemical failure free survival. The confidence of accurate targeting, however, is a vital step preceding dose escalation.

Disadvantages include patient discomfort in an invasive implantation procedure, the requirement of an additional appointment for the implantation at least a week prior to planning CT, and the additional services of radiology and urology personnel for the TRUS during the implantation procedure.[15] Patient discomfort was assessed through a self-assessed patient questionnaire. The median comfort rating of 4 indicates that the procedure was tolerable. At consent and in the patient information sheet, patients were advised that the implantation procedure would be comparable to their biopsy, in terms of comfort, and whether this influenced their perception of the procedure is unknown.

Fiducial marker migration has been reported on in previous studies and has generally been found to be not significant when correctly implanted.[5,16] The ACCULOC® fiducial markers used for this study have a cross-hatched surface to minimise migration. Our study assumed that no detectable migration occurred.

The department treats an average of 250 to 300 prostate patients a year, with an average 45% of those from outside of the immediate local area. With close to half of the prostate patients living outside of the immediate service area, the inconvenience of travelling to the centre for marker implantation a week before simulation needs to be taken into consideration. The possibility of implantation occurring within the patient's home town, or a centre closer to home is to be evaluated. This would require further training of urologists within the greater service area.

Limitation of sample size

This feasibility study was limited to 10 patients due to the donation of the fiducial markers by the distributing company (CMS Alphatech, Missouri, USA). Ideally, a larger sample size would be beneficial, with sample size calculations showing that to enable the detection of a difference in the prostate displacement of 5 mm compared to bony anatomy, with a power of 80% and a 2-sided alpha level of 5%, 34 patients are required, with the assumption that standard deviation of prostate displacement is 5.6 mm.[5] Further data will be acquired from a phase two study.

Future directions

Should online correction be implemented, departmental tolerance will be re-assessed. While currently a 5 mm action tolerance, a 3 mm tolerance would be beneficial, however the interuser variability is a limiting factor in this and would have to be addressed. This study did not investigate intra-fraction motion of the prostate, another consideration for accurate treatment delivery.

This study did not investigate whether a patient's average daily displacement differed from the commencement of treatment to the end of their course of treatment. This may be an area for future studies as acute side effects such as diarrhoea which usually begin to occur within the latter half of treatment may influence timeline trends.

With the introduction of Cone Beam CT (CBCT) capabilities to the department, comparison of CBCT, an alternative method of visualising the prostate position, and fiducial markers is required to determine the optimal method of prostate localisation, in both accuracy and efficiency.

While many centres world wide have been using online correction with fiducial markers in prostate treatments, as yet there is little long-term data available to confirm the benefit in terms of lessening long term side effects, and improving local control.

Conclusion

This study supports the growing body of evidence that there is benefit in the use of daily imaging with gold seed fiducial markers within the prostate, for more accurate treatment.

This study demonstrates the feasibility of implementing fiducial markers within the department as a means of accurately improving treatment targeting with daily imaging and correction, therefore minimising the effect of interfractional prostate motion.

With the use of gold seed fiducial markers being adopted by many centres, evidence on the improvement of long-term side effects and local control is awaited.

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The authors
AL Brown BAppSc (MRT)
EL Day MAppSc (MRS)

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