A comparison of the use of bony anatomy and internal markers for off-line verification and an evaluation of the potential benefit of on-line and off-line verification protocols for prostate radiotherapy.

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Running title: Off-line and on-line verification protocols for prostate cancer radiotherapy

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Abstract.

Background and Purpose: To evaluate the utility of intra-prostatic markers in the treatment verification of prostate cancer radiotherapy. Specific aims were:-

(i) to compare the effectiveness of off-line correction protocols, either using gold markers or bony anatomy.
(ii) to estimate the potential benefit of on-line correction protocol’s using gold markers
(iii) to determine the presence and effect of intrafraction motion.

Patients and Methods: 30 patients with 3 gold markers inserted had pre and post treatment images acquired and were treated using an off-line correction protocol and gold markers. Retrospectively, an off-line protocol was applied using bony anatomy and an on-line protocol using gold markers.

Results: The systematic errors were reduced from 1.3, 1.9 and 2.5mm to 1.1, 1.1 and 1.5mm in the RL SI and AP directions respectively using the off-line correction protocol and gold markers instead of bony anatomy. The subsequent decrease in margins was 1.7, 3.3 and 4mm in the RL SI and AP directions respectively. An off-line correction protocol combined with an on-line correction protocol in the first four fractions reduced random errors further to 0.9, 1.1, 1.0mm in the RL, SI and AP directions respectively. A daily on-line protocol reduced all errors to <1 mm. Intra fraction motion had greater impact on the effectiveness of the on-line protocol than the off-line protocols.

Conclusion: An off-line protocol using gold markers is effective in reducing the systematic error. The value of on-line protocols is reduced by intrafraction motion.

Keywords: Prostate cancer; Radiotherapy; Electronic portal imaging; organ motion; intrafraction motion
Introduction

Radical radiotherapy for localised prostate cancer relies on the delivery of a tumouricidal radiation dose to the prostate, while limiting the dose received by organs at risk. The adoption of conformal planning techniques has been shown to reduce rectal and bladder toxicity for a given prescribed dose, without reducing treatment efficacy (1). This has permitted dose escalation, with both improved biochemical control rates and acceptable, although increasing treatment-related morbidity (2). The use of intensity modulated radiotherapy (IMRT) may enable even greater sparing of organs at risk, making increased dose escalation a realistic option or permitting a further reduction in treatment related side effects.

However target volume shaping and normal tissue avoidance is dependant on accurate target (prostate) localisation. The prostate is a mobile organ and localisation using bony landmarks has inherent limitations. This leads to the necessity of designing a planning target volume (PTV) with adequate margins to encompass prostate movement (3).

Conventionally, verification of the accuracy of radiotherapy treatment set-up relies on mega-voltage imaging to check the position of the pelvic bony anatomy, since the prostate itself is not visualised. Methods involving soft tissue imaging are currently under investigation. The use of ultrasound in imaging the prostate has been studied but its value remains controversial (4,5,6,7,8,9,10). The issues yet to be clarified are the differences between the ultrasound image and the CT image in determining the prostate anatomy and the possibility that the pressure of the probe shifts the prostate position between alignment and treatment. Cone beam CT is being explored but involves purchasing additional equipment for each linear accelerator and increased time on the treatment unit. An alternative approach, which is already routine in clinical practice in several centres (11,12,13,14,15) is to use fiducial marker seeds implanted within the prostate. These markers can be visualised on mega-voltage imaging, thus enabling verification of prostate, rather than bony landmarks position. This has the potential to improve the accuracy of prostate radiotherapy in two ways: First, the identification and correction of systematic set-up errors can be based on prostate, rather than pelvic bone, position. Second, there is potential for on-line alteration of treatment set-up in response to fiducial marker position which would reduce the
random error. Hence the planning target volume (PTV) could be reduced. Given the dose-volume effect for rectal morbidity (16,17), this reduction in the PTV should enable further dose escalation with acceptable toxicity, and hence improve the therapeutic ratio for prostate radiotherapy.

Other authors have shown that the use of gold markers is clinically feasible (18,11,19), that there is no significant marker migration within the prostate(20,21,22) and that there is independent prostate movement (23,24) relative to bony anatomy. The consequence of using bony anatomy for prostate position verification instead of gold markers using an off-line protocol has also been shown [29,24]. Potentially, the use of an on-line protocol will reduce the random and systematic error further. However any potential benefit will be limited by the presence of intrafraction motion. Intrafraction motion has been much less investigated than interfraction motion. A summary of intrafraction motion studies can be found in Ghilezan et al (25). Intrafraction motion has been assessed by:

(i) Imaging the prostate during treatment with the use of markers and fluoroscopy. Generally the time frames used were very short (10-20secs)(26,27,28,29) except for one study where the time frame was 2-3 mins(30).

(ii) Using the treatment beams to determine the position of the prostate at the beginning and end of treatment. The 3D position of the prostate is calculated as an average of the first 2 beams and the last 2 beams(31,23).

(iii) Using cine MR. This tended to use longer time frames (6-9mins) which better represents treatment times(32,33).

Only two studies have performed pre and post treatment images, one using ultrasound (34) and the other markers (35).

This paper compares set errors using skin marks only with off-line correction protocols using bony anatomy and gold markers and calculates the respective PTV margins needed to deliver a 95% dose ($D_{95}$) to the 95% CTV volume ($V_{95}$) for 90% of the patients (3). The proportion of patients who have benefited from using gold markers as opposed to bony anatomy for treatment verification is calculated. To further evaluate the effectiveness of
correction protocols we have compared a combined on-line and off-line protocol with the above protocols. However, the presence of intrafraction motion will affect the efficacy of correction protocols and hence we determined any movement in the time between the first beam on and last beam off and the effect of this intrafraction movement on the protocols. Our experiences with gold marker insertion are also reported.

Materials and Method
Patients referred for radical radiotherapy to the prostate were invited to participate in this study and informed consent obtained. Three gold markers, 1mm diameter x 8mm length, were inserted into the prostate under trans-rectal ultrasound guidance and antibiotic cover prior to adjuvant hormone therapy. The study had been approved by the research and ethics committees of the Royal Marsden NHS Foundation Trust and Institute of Cancer Research.

Helical CT scans (GE QXI high speed) were acquired and reconstructed using 2.5mm slice thickness. Immobilisation was achieved using ankle stocks and knee supports and patients were scanned and treated with a partially filled, comfortably full bladder (36). 3 field conformal plans were produced using the Pinnacle treatment planning system and anterior and lateral digitally reconstructed radiographs (DRR's) were created to be used as reference images.

Orthogonal electronic portal images (EPI) were acquired to verify the isocentre position prior to and after treatment delivery using the Elekta view GT (Asi EPID). These verification images were acquired for the first 4 days of treatment and once a week thereafter with minimal dose (2 MU). The pre treatment images were matched to the gold markers using manual template matching and an off-line protocol was used to identify and correct for systematic treatment set-up errors (37). That is, the systematic error was determined after 4 fractions and if this error was greater than 2 mm in any direction a couch correction shift was performed. A 3mm tolerance was used for the subsequent weekly images.
To identify if there was any marker migration during the treatment schedule the intermarker distances were measured on fractions 1, 2, mid treatment and end of treatment. Marker positions were identified using in-house software (38). The centre of the mass of the markers and the distances between each marker was calculated to determine if one marker migrated relative to the others.

The set up displacement data was then used to calculate the following (Figure1):-

(i) The effectiveness of an off-line correction protocol based on gold markers. The random error ($\sigma_{gm}$) and systematic error ($\Sigma_{sm}$) of the group of 30 patients using the off-line protocol and gold markers was calculated from the treatment set-up data. That is the systematic error ($\Sigma$) for the group of patients is the standard deviation (SD) of the distribution of the average set-up displacements per patient. The random error ($\sigma$) is the SD of the patients’ set-up displacements averaged over all the patients in the group (39).

(ii) Analysis of field displacement with respect to gold marker and bony anatomy position. The pre treatment images were retrospectively matched using bony anatomy to compare the displacements determined using gold markers with bony anatomy.

(iii) The set-up errors if no correction protocol had been used. All measurements were then retrospectively corrected for the fact that off-line corrections may have been made, resulting in uncorrected data i.e as if the patients had been treated using skin marks only and random error ($\sigma_{sm}$) and systematic errors ($\Sigma_{sm}$) calculated.

(iv) The effect on the prostate if bony anatomy was used to calculate field displacement. Using the uncorrected data each patients individual systematic error was calculated after 3 fractions using bony anatomy. If this error was greater than 2mm a virtual correction was applied and the position of the gold markers recorded. The group random ($\sigma_{ba}$) and systematic errors ($\Sigma_{ba}$) errors were calculated.

(iv) The effect of an on-line protocol. An on-line protocol was used retrospectively by eliminating any displacement > 2mm and the patient group random ($\sigma_{ol}$) and systematic errors ($\Sigma_{ol}$) errors calculated.

(v) Inter-fraction and Intra-fraction motion. The post-treatment images were matched retrospectively to gold markers and bony anatomy to determine the post treatment
displacements. The total inter-fraction and intra-fraction motion was determined by calculating the difference in position of the gold markers pre and post treatment.

The bony anatomy displacements were subtracted from the gold marker displacements to obtain the prostate movement relative to pelvic bone.

(vi) The effect of movement during treatment. The intra-fraction motion was added to the set-up errors after the off-line and the on-line corrections had been made. The subsequent patient group random ($\sigma_{\text{offl}}$, $\sigma_{\text{onll}}$) and systematic errors ($\Sigma_{\text{offl}}$, $\Sigma_{\text{onll}}$) errors calculated.

(vi) The effect of using an off-line and on-line protocol. In addition to the off-line protocol used for treatment, as described above, an on-line protocol was applied retrospectively to the first four fractions correcting for any displacement > 2mm. The patient group random ($\sigma_{\text{olof}}$) and systematic errors ($\Sigma_{\text{olof}}$) errors were then calculated.

(vi) The margins required for set up displacement using the protocols above were calculated using Van Herk's formula (3). However a caveat must be added that this is for theoretical comparison and these margins would be too small to use clinically as they do not take into account rotation or prostate deformation (3). The margins arising from uncertainties in outlining and planning would also need to be added for clinical use.

Results

Marker insertion

30 patients had 3 gold markers inserted. All patients tolerated this procedure. At the time of treatment 3 patients had only 2 seeds remaining in the prostate. Two of these patients were among the first five patients in the study. The median time between the gold marker insertions and the radiotherapy CT scan was 60.5 days (range 3-145 days).

The intermarker distances were measured on fractions 1, 2, mid treatment and end of treatment. 3 (10%) patients had movements > than 2mm between the markers. The distance between the markers did not increase or decrease consistently with time.

Analysis of field displacement with respect to gold marker and bony anatomy positions

A total of 408 fractions were imaged (mean 14 images per patient; range 8-21images). Since both anterior and lateral orthogonal images were obtained, the superior inferior direction was
measured from both planes. There was a strong correlation between the measurement in SI direction from each plane \((r=0.8)\) therefore the measurements were averaged and the mean SI measurement was used. There were 382, 395 and 338 pairs of pre treatment images available for comparison in the RL, SI and AP direction respectively.

Scatter plots of the set-up displacement measured from gold markers (x axis) and bony anatomy (y axis) are shown in Figures 2a, 2b and 2c. There was close correlation between gold markers and bony anatomy set-up displacements in the right left (RL) direction \((r=0.9)\), demonstrating a strong relationship between bony anatomy and prostate position. The correlation between gold markers and bony anatomy set-up displacements in the superior–inferior (SI) and anterior-posterior (AP) direction was less strong, \(r=0.6\) and \(r=0.5\) respectively.

Translating these results into clinical effect, the number of fractions where a different action would have been taken using gold markers as opposed to bony anatomy if an on-line protocol was used is shown in Table 1a, 1b and 1c. The threshold of a difference was set as greater than 2mm. 19% 46% and 45% of the fractions in the RL, SI and AP direction respectively would have resulted in a different action when using bony anatomy as opposed to gold markers. The magnitude of the differences were equivalent right to left and anterior to posterior but in the SI direction there were more movements superior than inferior.

The systematic error calculated using gold markers rather than bony anatomy was >2mm different in at least one direction in 50% of patients. Four of the 30 patients (13%) had a systematic error with a difference >5mm using gold markers as opposed to bony anatomy; one patient in the SI direction and three patients in the AP direction.

*Interfraction prostate motion*

The SD of the prostate interfraction movement was greater in the AP direction (mean -0.3 +/- 3.7 mm) than the RL and SI directions (mean -0.1mm +/- 2.5mm and mean 0.6mm +/- 2.6mm respectively). 16% of these AP movements were >5mm, 7.5% posterior and 8.6% anteriorly. The independent (i.e corrected for changes in bony anatomy position) interfraction prostate
movement was 0.0mm +/- 1.1mm, 1.0 mm +/- 2.4mm and -0.1mm +/- 3.5mm in the RL, SI and AP directions respectively. The direction of the prostate movement was again equivalent in the AP and RL direction but predominantly superior in the SI direction. The bony anatomy interfraction movement showed the same trend though the difference was less marked with a mean 0 +/- 2.6, -0.2 +/- 2.7 and -0.4 +/-3.5mm in the RL, SI and AP directions respectively.

Intrafraction movement

There were 219 anterior pairs of images and 210 lateral pairs of images available for matching. The difference in position of the markers between images prior to treatment delivery and post treatment delivery was determined. The total intrafraction movement observed was 0.2mm +/- 1.3mm, -0.1mm +/- 1.8mm, -0.1 mm +/- 2.0mm in the RL, SI and AP directions respectively. To determine the independent prostate movement (i.e corrected for changes in bony anatomy position) the bony anatomy movement was subtracted from the gold marker displacements. The independent intrafraction prostate motion was -0.1 mm +/- 1.2mm, 0.5 mm +/- 2mm, 0mm +/- 2.5mm in the RL, SI and AP directions respectively.

Comparison between an off-line and on-line protocols using bony anatomy and gold markers.

The systematic and random errors of prostate, determined from the position of the gold markers, in the group of 30 patient's were calculated when either skin marks, bony anatomy or gold markers were used to determine the set-up displacements (Table 2). Using an off-line correction protocol and gold markers the systematic errors were reduced with the greatest effect in the AP direction as compared to using either bony anatomy (31% reduction) or skin marks (58% reduction).

When using the off-line protocol and bony anatomy to determine the systematic error, the AP set-up displacement remained > 5mm in 21% of fractions compared to 16% if gold markers had been used. 56% of these fractions occurred in 5 of the patients.

Using an on-line protocol for the first four fractions prior to correcting for the systematic error with an off-line protocol reduced the systematic error to < 1.1mm in all directions. An on-line
protocol reduced the systematic error further to < 0.5mm and the random error to < 0.8mm in all directions (Table 3).

However, accounting for the intrafraction motion had greater consequence on the on-line correction protocol, where the random and systematic error increased, as compared to the off-line correction protocol and the on-line for first four fractions and offline protocol (Table 3).

Discussion
The clinical implementation of using gold markers for prostate position verification was found to be feasible. The markers were visible on both the anterior and lateral images. Three patients 'lost' a marker prior to treatment. There is evidence of a learning curve associated with the insertion of the markers since two of the three patients were among the first five patients in the study and this observation is in agreement with Henry et al (40). In addition in the three patients where the distance between the markers changed by more than 2mm, one of the markers had been placed very posterior and close to the rectal wall. This could have resulted in a less stable position with the markers undergoing extreme rotation and the distance between the centres would have varied giving the impression of marker migration. There was no indication of either prostate swelling (increased separation of markers) or shrinking (decreased separation of markers) which might have been caused by prostate swelling or constriction due to radiotherapy or continual hormone therapy respectively. Where the position of the markers within the prostate has been stated in other studies it is either in both lobes and apex, when there were 3 markers used (27,19), or at the base and the apex (40,41,20,22). Only one study was specific in stating that the markers should be at some distance from the rectal wall and urethra (11) which is in accordance of our experience. There is a case for guidelines to be developed regarding best position of markers. The absence of marker migration during treatment agrees with that in previous studies (12,11,22,19,20).

The existence of prostate movement relative to bony anatomy is well established. However, many departments use bony anatomy for prostate cancer treatment verification. The PTV margins calculated in this study by using the formula $2.5\Sigma + 0.7\sigma$ and using bony anatomy for set-up correction was 0.4mm, 2.1mm and 2.4mm larger in the RL, SI and AP directions.
respectively than the margin needed when using gold markers. The use of gold markers would benefit the patients by potentially reducing rectal toxicity since the greatest reduction was seen in the AP direction. In addition because of the independent prostate movement 45% of the patients would have been moved incorrectly in the AP direction if an on-line protocol using bony anatomy had been used with 4 (13%) of patients being moved >5mm incorrectly if bony anatomy and an off-line protocol had been used to establish the systematic error. Using an on-line correction protocol in 23 patients Chung et al (18) showed that the maximum displacements were in the AP direction (10-11mm compared to 7mm-9mm in the SI direction). Adjustments of 5mm or more were necessary in 11% of occasions which is comparable with our findings where 16% of events were >5mm in the AP direction. This leads us to suggest that the common practice of reducing the posterior margin when using bony anatomy for verification must be done with caution. It will have more effect in some patients than others as the majority of events >5mm in the posterior direction occurred in five patients out of the cohort of 30. Nederveen et al also found that the use of a bony anatomy protocol increased the set-up error in six patients out of a cohort of 23 (13). For two patients the direction was in the AP direction and for four patients, the SI direction. It is surprising that there were more disagreements in the SI direction rather than in the AP but is explained by the poor correlation in Nederveen's study between marker and bony anatomy in the SI direction \( r=0.08 \) as compared to the correlation in the RL and AP direction \( r=0.91 \) and \( r=0.86 \). Why this should be so is not clear. Using the pubic symphysis from the anterior field to determine the bony anatomy in the SI direction and the CT slice thickness 3mm should have produced a stronger correlation. Notwithstanding this discrepancy, methods need to be explored to identify and target this group of patients who fall at the extremes of the distribution. Ghilzean et al (42) theoretically assessed the clinical benefit of improving precision and accuracy of treatment delivery and also concluded that it would be clinically efficient to select patients who might receive maximum benefit from an on-line approach.

The inter fraction movement and the effectiveness of an off-line protocol reported here agrees with other studies. Boer et al (41) used a NAL protocol and halved the systematic displacements. We reduced the systematic displacements by 39%, 54% and 58% in the RL, SI and AP directions respectively. Van Lin et al (43) also used a NAL protocol in a study to evaluate the
effectiveness of an endorectal balloon. In the group of 30 patients without the balloon the systematic displacements were reduced by 44% ,58% , 62% which is a comparable with our study. Nederveen et al (13) used the shrinking action level protocol (SAL) and the systematic error reduced from 2.4mm, 4.4mm and 3.7mm to 0.6mm, 0.9mm and 0.6mm in the RL, SI and AP direction respectively. This is a much smaller systematic error than seen here but involved a greater workload. The patients were imaged daily and the protocol applied throughout the entire treatment. However, a direct comparison of the SAL and the NAL protocol using an average of 10 imaged fractions per patient found the NAL protocol to be more efficient in terms of number of images per reduction in systematic error (37). We clinically implement the NAL protocol in our department based on this study.

In addition to the off-line protocols, we retrospectively applied an on-line protocol where any displacement >2mm was corrected. We found using an on-line protocol correcting any displacements <2mm that the random and systematic errors were reduced to <1mm. This is comparable with Chung et al (18) who used an on-line protocol correcting any displacement <3mm. The random and systematic components measured at the centre of mass of the gold grains reduced from mean -0.3mm (SD 3.2mm) and -0.5mm (SD 2.5mm) to mean 0 (SD 1.3mm) and mean -0.1mm (SD 1.2mm) in the AP and SI direction respectively.

The potential of an on-line protocol is also limited by any intra fraction motion present. The majority of studies investigating intra fraction motion have concentrated on the motion while the treatment beam is on. These movements are often momentary and have been found, by imaging with MRI, to last a mean time period of 20secs (33). Whilst the extent of movements during this time will have an impact on dose delivered to the prostate, we have the measured the prostate shift at the beginning and the end of the treatment which will affect the potential benefit of an on-line correction protocol. Table 4 shows a comparison of our results with other studies. Schallenkamp et al (23) and Aubry (31) determined the difference between the average of the position of the prostate in the first two and the last two beams as intrafraction motion. The SD we found was greater in the SI and AP directions. By averaging the position of the prostate in the first two beam and the last two beams it is possible that intra fraction motion is over or under
estimated. Any movement between the two beams would have been averaged out. Cheung et al. (35) imaged before and after treatment and the resulting averages of motion are closer in magnitude to ours however the SD in the AP direction is still greater in our study. This may be due to the patient’s preparation. The patients were asked to empty their rectum prior to planning and treatment in Cheung’s study; we currently do not give bowel advice to our patients. An empty rectum has been correlated with less intrafraction prostate movement in studies using cine MRI (33). Ghilzean et al (25) imaged six patients on 3 days also using cine MRI over a time period of 20mins. The time frame for a 10% probability of moving >3mm increased from ~1min in the case of a full rectum to 20 min in the case of a empty rectum.

We have translated the consequence of intrafraction motion on the PTV margins needed necessary to cover the CTV. Cheung et al found that the average patient specific PTV margin of 3mm (range 2-5mm), 3mm (range 2-7mm) and 4mm (range 2-8mm), this correspond well with our calculated margin of, 3.2, 3.4 and 3.5mm all in the RL, SI and AP direction respectively although the range is large (35). However as Chung et al point out, the respiratory motion and EPID motion was counted as separate movements but it is possible that some of the respiratory motion was captured by the EPIDs which would have increased the movement and hence the margins. Nederveen et al imaged 10 patients during the treatment time for a time span of 2-3 min (30). They found that as the time frame increased the displacements increased. The displacements were larger in the SI and AP direction and were predominantly anterior and superior. Our displacements were equally distributed anterior and posteriorly but were more superior than inferior. Nederveen concluded that the intra fraction prostate motions did not result in margins larger than 1mm provided that the verification is performed at time intervals of 2-3 min. This would be ideal solution but not practical in many departments. From our study we would propose that an on line protocol should not be used with set-up margins less than 4 mm (Table 3).

A daily on line protocol is also resource intensive. A combination of an on-line and off-line protocol may be a more efficient method. Using an on-line protocol in the first four fractions would reduce the systematic and random error while providing enough information to subsequently use
an off line protocol. Van de Heuval (44) investigated the effect of applying an on-line protocol to the first four fractions in addition to the off-line protocol and found a slight decrease in the random error but the systematic error remained essentially unchanged and hence there was no significant change in the margin. Van de Heuval postulated that the estimation of the systematic error was flawed because of the small number of fractions used. It may have also been due to only 10 patients in the study. We found that using this method the greatest advantage was in the AP direction where the systematic error was reduced by 0.5mm and the random error by 0.9mm resulting in a 1.6 mm reduction in margin. Another study in a large group of patients has shown that an adapted Shrinking Action Level (SAL) protocol was the most effective method of correction compared to a weekly SAL, regular SAL and NAL protocols(45).

Conclusion
The use of gold markers for prostate position verification is clinically feasible and there is minimal marker migration. The off-line NAL protocol applied to the gold markers reduces systematic error with the greatest benefit in the AP direction. However if bony anatomy is used for verification margins need to be larger particularly in the AP direction (8.4mm compared to 5.8mm). There was a group of patients where using bony anatomy instead of gold markers had more detrimental effect than the others. A combination of an online and off line correction protocol did reduce the systematic and ransom errors further but this did not
substantially reduce the margins required when intrafraction motion was considered. An on-line protocol was effective but was more sensitive to the presence of intrafraction motion. To continue to improve the accuracy of treatment delivery methods of reducing intrafraction motion must be investigated. In addition it may be possible to identify and target the patients who would benefit most from further intervention.
Patients treated using an off-line verification protocol based on gold markers and pre treatment images.

- Set-up corrections subtracted to obtain set-up using skin marks only.
  - Images retrospectively matched using bony anatomy
  - Patient group systematic ($\Sigma_{gm}$) and random ($\sigma_{gm}$) error calculated
    - Correlation between gold marker and bony anatomy set-up displacements calculated
    - Bony anatomy displacements subtracted from gold marker displacements to calculate interfraction prostate motion relative to bone
  - Individual patient systematic error calculated after 3 fractions using bony anatomy
    - Applied to uncorrected data
  - Patient group systematic ($\Sigma_{sm}$) and random ($\sigma_{sm}$) errors calculated
- Patient group systematic ($\Sigma_{ba}$) and random ($\sigma_{ba}$) error calculated
- On-line corrections applied

Patient group $\Sigma_{ol}$ patient group
Figure 2a. The difference between the Gold markers (x axis) and the Bony anatomy (y axis) in the Right-Left Direction with an inset histogram showing the deviation of gold marker position from bony anatomy position.
Fig 2b. The difference between the Gold markers (x axis) and the Bony anatomy (y axis) in the Superior-Inferior Direction with an inset histogram showing the deviation of gold marker position from bony anatomy position.
Fig 2c. The difference between Gold markers (x axis) and the Bony anatomy in the Anterior-Posterior direction with an inset histogram showing the deviation of gold marker position from bony anatomy position.
Table 1a.
No of fractions in R-L direction where the bony anatomy displacement and the gold marker displacement resulted in the same action

<table>
<thead>
<tr>
<th>Gold markers</th>
<th>Displacement</th>
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<th>In Tolerance</th>
<th>&gt;2mm</th>
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<tr>
<td>In Tolerance</td>
<td></td>
<td>22</td>
<td>195</td>
<td>15</td>
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<tr>
<td>&gt;2mm</td>
<td></td>
<td>0</td>
<td>15</td>
<td>59</td>
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Table 1b.
No of fractions in Superior- Inferior direction where the bony anatomy displacement and the gold marker displacement resulted in the same action

<table>
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<th>In Tolerance</th>
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<td>68</td>
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<tr>
<td>In Tolerance</td>
<td></td>
<td>15</td>
<td>135</td>
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<tr>
<td>&gt;2mm</td>
<td></td>
<td>0</td>
<td>28</td>
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Table 1c.
No of fractions in Anterior-Posterior direction where the bony anatomy displacement and the gold marker displacement resulted in the same action

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<th>In Tolerance</th>
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<td>5</td>
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<tr>
<td>In Tolerance</td>
<td></td>
<td>31</td>
<td>99</td>
<td>36</td>
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<td>&gt;2mm</td>
<td></td>
<td>12</td>
<td>31</td>
<td>30</td>
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</table>

Where minus = Right, Inferior and Posterior
Table 2. The effect of no correction protocol, an off-line correction protocol using bony anatomy and an off-line protocol using gold markers.

<table>
<thead>
<tr>
<th>Correction protocol</th>
<th>Reference used</th>
<th>Error/Margin</th>
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<th>S-I (mm)</th>
<th>A-P (mm)</th>
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<td>None</td>
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<td>$\Sigma_{sm}$</td>
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<td>3.6</td>
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<tr>
<td>None</td>
<td>Skin marks</td>
<td>$\sigma_{sm}$</td>
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<td>2.2</td>
<td>2.8</td>
</tr>
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<td><strong>None</strong></td>
<td><strong>Skin marks</strong></td>
<td>*Margin</td>
<td>6</td>
<td>7.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Off-line</td>
<td>Bony anatomy</td>
<td>$\Sigma_{ba}$</td>
<td>1.3</td>
<td>1.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Off-line</td>
<td>Bony anatomy</td>
<td>$\sigma_{ba}$</td>
<td>2.2</td>
<td>2.2</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Off-line</strong></td>
<td><strong>Bony anatomy</strong></td>
<td>*Margin</td>
<td>4.7</td>
<td>6.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Off-line</td>
<td>Gold markers</td>
<td>$\Sigma_{gm}$</td>
<td>1.1</td>
<td>1.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Off-line</td>
<td>Gold markers</td>
<td>$\Sigma_{gm}$</td>
<td>2.2</td>
<td>2.1</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Off-line</strong></td>
<td><strong>Gold markers</strong></td>
<td>*Margin</td>
<td>4.3</td>
<td>4.2</td>
<td>6.0</td>
</tr>
</tbody>
</table>

$\Sigma$ = systematic error

$\sigma$ = random error

R-L = right-left direction

S-I = superior-inferior direction

A-P = anterior–posterior direction

* Margin calculated using Van Herk formula $2.5 \Sigma + 0.7 \sigma$
Table 3. The effect of an on-line protocol, an on-line and off-line correction protocol and intrafraction motion using gold markers.

<table>
<thead>
<tr>
<th>Correction protocol</th>
<th>Reference used</th>
<th>Error/Margin</th>
<th>R-L (mm)</th>
<th>S-I (mm)</th>
<th>A-P (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-line Gold markers</td>
<td>Σol</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>On-line Gold markers</td>
<td>σol</td>
<td>0.8</td>
<td>0.7</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td><strong>On-line</strong> Gold markers</td>
<td>*Margin</td>
<td>1.3</td>
<td>1.2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>On-line for 4 fractions + Off line thereafter Gold markers</td>
<td>Σolof</td>
<td>0.9</td>
<td>1.1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>On-line for 4 fractions + Off line thereafter Gold markers</td>
<td>σolof</td>
<td>1.9</td>
<td>1.8</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td><strong>On-line for 4 fractions</strong> + Off line thereafter Gold markers</td>
<td>*Margin</td>
<td>3.6</td>
<td>4.0</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Off-line including intrafraction motion</td>
<td>Σolif</td>
<td>1.1</td>
<td>1.4</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Off-line including intrafraction motion</td>
<td>σolif</td>
<td>2.1</td>
<td>2.1</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td><strong>Off-line including intrafraction motion</strong></td>
<td>*Margin</td>
<td>4.2</td>
<td>5.0</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>On-line including intrafraction motion</td>
<td>Σ</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>On-line including intrafraction motion</td>
<td>σ</td>
<td>1.2</td>
<td>1.6</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td><strong>On-line including intrafraction motion</strong></td>
<td>*Margin</td>
<td>3.0</td>
<td>3.4</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>On-line for 4 fractions + Off-line including intrafraction motion Gold markers</td>
<td>Σ</td>
<td>0.9</td>
<td>1.4</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>On-line for 4 fractions + Off-line including intrafraction motion Gold markers</td>
<td>σ</td>
<td>1.9</td>
<td>2.1</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td><strong>On-line for 4 fractions</strong> + Off line including intrafraction motion Gold markers</td>
<td>*Margin</td>
<td>3.6</td>
<td>5.0</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

Σ = systematic error
σ = random error
R-L = right left direction
S-I = superior inferior direction
A-P = anterior – posterior direction

* Margin calculated using Van Herk formula 2.5 Σ + 0.7 σ
Table 4. Intrafraction motion measured in Right-Left (RL), Superior-Inferior(SI) and anterior-posterior (AP) directions

<table>
<thead>
<tr>
<th>Author</th>
<th>Technique</th>
<th>RL movement Mean (SD) mm</th>
<th>SI movement Mean (SD) mm</th>
<th>AP movement Mean (SD) mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schallenkamp</td>
<td>Difference between the average of prostate position between first two and last two beams</td>
<td>0.1 (0.3)</td>
<td>0.4 (0.2)</td>
<td>0.1 (0.7)</td>
</tr>
<tr>
<td>(23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aubry (31)</td>
<td>Difference between the average of prostate position between first two and last two beams</td>
<td>0.2 (0.8)</td>
<td>0 (1.1)</td>
<td>0.2 (0.6)</td>
</tr>
<tr>
<td>Cheung (35)</td>
<td>Pre and post treatment images</td>
<td>0.14 (0.92)</td>
<td>0.45 (1.27)</td>
<td>0.72 (1.8)</td>
</tr>
<tr>
<td>McNair</td>
<td>Pre and post treatment images</td>
<td>0.2 (1.3)</td>
<td>-0.1 (1.8)</td>
<td>-0.1 (2.0)</td>
</tr>
</tbody>
</table>
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