Original Research Article

The accuracy of Magnetic Resonance – Cone Beam Computed Tomography soft-tissue matching for prostate radiotherapy

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ABSTRACT

Background and purpose: Magnetic Resonance (MR)-Only radiotherapy requires a method for matching image with on-treatment Cone Beam Computed Tomography (CBCT). This study aimed to investigate the accuracy of MR-CBCT soft-tissue matching for prostate MR-only radiotherapy.

Materials and methods: Three patient cohorts were used, with all patients receiving MR and CT scans. For the first cohort (10 patients) the first fraction CBCT was automatically rigidly registered to the CT and MR scans and the MR-CT registration predicted using the MR-CBCT and CT-CBCT registrations. This was compared to the automatic MR-CT registration. For the second and third cohorts (five patients each) the first fraction CBCT was independently matched to the CT and MR by four radiographers, the MR-CBCT and CT-CBCT matches compared and the inter-observer variability assessed. The second cohort used a CT-based structure set and the third a MR-based structure set with the MR relabelled as a 'CT'.

Results: The mean difference between predicted and actual MR-CT registrations was $\Delta R_{All} = -0.1 \pm 0.2$ mm (s.e.m.). Radiographer MR-CBCT registrations were not significantly different to CT-CBCT, with mean differences in soft-tissue match $\leqslant 0.2$ mm and all except one difference . This was less than the MR-CBCT inter-observer limits of agreement [3.5, 2.4, 0.9] mm (vertical, longitudinal, lateral), which were similar ($\leqslant 0.5$ mm) to CT-CBCT.

Conclusions: MR-CBCT soft-tissue matching is not significantly different to CT-CBCT. Relabelling the MR as a 'CT' does not appear to change the automatic registration. This suggests that MR-CBCT soft-tissue matching is feasible and accurate.

1. Introduction

Magnetic Resonance (MR)-Only radiotherapy enables the superior soft-tissue contrast of MR [1] to be used for organ delineation without the uncertainties of a MR-Computed Tomography (CT) registration [2]. MR-only radiotherapy requires a method of generating a synthetic CT (sCT) from the MR that can be used for radiotherapy dose calculations [3]. Commercial solutions with high dosimetric accuracy are now being used clinically in the treatment of prostate cancer [4,5].

In a MR-CT fusion workflow the CT is not just used for organ delineation and treatment planning but also as the reference image for on-treatment image matching, typically using kilovoltage planar or Cone Beam CT (CBCT) images [6]. So far, clinical implementations of MR-only radiotherapy for prostate cancer have used implanted fiducial markers for image guidance with the markers digitally added to the sCT

[7,4,5]. However a significant number of centres do not use fiducial markers and employ CBCT soft-tissue matching for prostate radiotherapy treatments (~60% of UK centres) [8]. Additionally, radiotherapy treatments of many other cancers are not conventionally performed with implanted fiducial markers. Therefore for MR-only radiotherapy to be used more broadly, it is essential that methods of on-treatment imaging matching to CBCT are developed.

Several studies have reported using sCTs as the reference image for CBCT matching for prostate cancer. Korhonen et al. reported mean differences in CT-CBCT and sCT-CBCT matches as $\leqslant 0.3$ mm in all directions [9]. Chen et al. found translational vector differences between CT-CBCT and sCT-CBCT automatic matches $\leqslant 1.08$ mm and rotational differences $\leqslant 1.1°$ for all three axes [10]. However the sCT soft-tissue image quality is often poor, which does not affect the dosimetric accuracy but would be detrimental for CBCT soft-tissue matching. This

suggests that the optimum reference image in a MR-only pathway would be the MR itself.

Two studies have investigated MR-CBCT matching for prostate MR-only radiotherapy [9,11]. Korhonen et al. found small ($\leqslant$ 1.5 mm) mean differences in each direction between automatic MR-CBCT and CT-CBCT registrations [9]. This did not assess the manual adjustments routinely performed by treatment radiographers in a soft-tissue match and so did not investigate the accuracy of the clinical process. Doemer et al. similarly found mean differences between manual MR-CBCT and CT-CBCT registrations to be $\leqslant$ 1.5 mm in each direction [11]. However, both studies only used a single observer and so were unable to compare the match differences with the inter-observer variability. In addition, both studies only used data from patients treated with a CT-based plan and contours, which may have affected the results. This study aimed to assess the accuracy of MR-CBCT soft-tissue matching for prostate MR-only radiotherapy using the clinical process with multiple observers using patient data from both CT-based and MR-based plans and contours.

2. Materials and methods

2.1. Patient data collection

This was a retrospective study including 20 patients treated with radiotherapy for prostate cancer at the Northern Centre for Cancer Care, Newcastle upon Tyne, UK. The patients were divided into three cohorts: registration commutation assessment (one), CT-based plan radiographer assessment (two) and MR-based plan radiographer assessment (three). Cohorts one (10 patients) and two (five patients) were selected retrospectively from all patients treated with radical radiotherapy for prostate cancer using a CT-based plan between 5 March and 3 April 2018. The following exclusion criteria were applied (number of patients excluded): MR not acquired (5), kilovoltage CBCT not acquired (4), patient external contour larger than MR field of view (1). Cohort three consisted of the first five patients treated using a novel MR-only radiotherapy pathway. The cohorts were similar, with median ages of 75, 72 and 71 years for cohorts one, two and three respectively.

All patients received planning MR (1.5 T Magnetom Espree, Siemens, Erlangen, Germany) and, the following day, CT (Sensation Open, Siemens) scans, performed on flat couch tops with local standard immobilisation. Prior to each scan patients underwent routine bladder and bowel preparation, consisting of a micro-enema application 60 min prior to the scan followed by bowel and bladder emptying 30 min later, then drinking 400 ml of water. Internal fiducial markers were not present. The MR images were acquired using a 6 channel flexible Body Matrix coil supported over the patient by an in–house manufactured coil bridge and the 24 channel Spine Matrix coil contained in the couch.

A SPACE (Sampling Perfection with Application optimised Contrasts using different flip angle Evolution) 3D turbo spin echo sequence was used, with a field of view of $450 \times 450 \times 180$ mm^3 with a voxel size $1.4 \times 1.4 \times 1.5$ mm^3. A bandwidth of 601 HzPixel^{-1} and the Siemens 3D distortion correction algorithm was used to minimise geometric distortion [12]. This was previously measured using a GRADE phantom (Spectronic Medical, Helsingborg, Sweden) [13], with maximum distortion $D_{max} = 2.5$ mm and 99 % of phantom markers having distortion $D < 2.0$ mm. The images were T2-weighted with echo time $TE = 211$ ms, repetition time $TR = 1500$ ms, flip angle $\alpha = 150°$ and acquisition time $T = 281$ s. For cohort three this MR image was used to create the sCT for dose calculations using MriPlanner (Spectronic). The CT images were acquired with a voxel size of $1.1 \times 1.1 \times 3$ mm^3 and a tube voltage of $V = 120$ kVp.

All patients were treated with 60 Gy in 20 fractions [14] with daily kilovoltage CBCT imaging using a TrueBeam STx (version 2.7 MR3, Varian Medical Systems, Palo Alto, USA). CBCT images were acquired with a voxel size of $0.9 \times 0.9 \times 2$ mm^3, field of view 46.5 cm and tube voltage $V = 125$ kVp.

2.2. Registration commutation assessment

The first fraction CBCT for patient cohort one was registered to the CT and to the MR using the automatic mutual information algorithm within RayStation (version 7, RaySearch Laboratories, Stockholm, Sweden). The registration used was a rigid registration with three degrees of freedom (translations only). The MR-CBCT and CT-CBCT registrations were then subtracted to predict a MR-CT registration using

$$\widehat{R}_{CT}^{MR} = R_{CBCT}^{MR} - R_{CBCT}^{CT}, \tag{1}$$

where R_B^A is the measured registration matrix registering the floating image A to the reference image B and $\widehat{R}_B^A$ is the predicted registration matrix between images A and B.

A rigid registration with three degrees of freedom between the MR and the CT was also calculated using the same methodology (R_{CT}^{MR}). This measured registration matrix was compared to the predicted registration matrix from Eq. (1) using $\Delta R_{CT}^{MR} = \widehat{R}_{CT}^{MR} - R_{CT}^{MR}$.

2.3. Radiographer matching assessment

Cohort two was used for the CT-based plan radiographer assessment. Each patient MR was automatically registered to the CT in RayStation focused on the Planning Target Volume (PTV), with 6 degrees of freedom (translations and rotations). The CT-based contours were transferred to the MR using this registration matrix. For cohort two the contours were a prostate-only Gross Tumour Volume (GTV) and prostate and seminal vesicles volume (GTV1), with three expansions used to create three PTVs [14]. The GTV and GTV1 were contoured on a separate small field of view MR scan acquired in the same session as the MR described in the methods and copied onto the CT. If there were discrepancies in soft-tissue anatomy between MR and CT (eg bladder filling) the GTV was then modified using the CT. The organs at risk (bladder and the rectum) were contoured directly on the CT. The first fraction CBCT was matched independently to the CT and to the MR using Aria (version 13.6, Varian) by four senior treatment radiographers with at least 3 years experience in prostate CT-CBCT matching. Each radiographer received additional training in MR prior to this study, consisting of MR pelvic anatomy outlining with a urology Consultant Clinical Oncologist, offline MR-CBCT matching experience followed by offline MR-CBCT matching benchmarking (see Fig. 1 for an example).

Two matches were carried out for each image set: an automatic match and a manual adjustment match based on soft-tissue information in the CBCT and the clinical delineations on the reference image (CT or MR). Both matches were translations only (three degrees of freedom). The starting point for each match was the centre of the CBCT image aligned to the treatment isocentre in the middle of the PTV. The centre of the CBCT image was the initial set-up to the treatment isocentre. The automatic registration algorithm within Aria is mutual information based and is the algorithm used by the TrueBeam during online treatment image matching.

The accuracy of MR-CBCT matching was assessed by using the CT-CBCT match as a gold standard and calculating the difference between each radiographer's MR-CBCT match and CT-CBCT match. The mean difference was assessed in each direction (vertical,longitudinal,lateral) and over all directions.

The MR-only plan assessment (cohort three) used the reverse process to cohort two, with the CT rigidly registered to the MR and the MR contours transferred to the CT. The contours were the same as cohort two but with the bladder and rectum contoured directly on the MR. In order for the MR to be used for online image guidance the MR was relabelled as a 'CT' since the current clinical versions of Aria and the TrueBeam will only accept a CT as the primary reference image. This involved changing the DICOM tags Modality, SOPClassUID and RescaleType to 'CT', '1.2.840.10008.5.1.4.1.1.2' and 'HU' respectively.
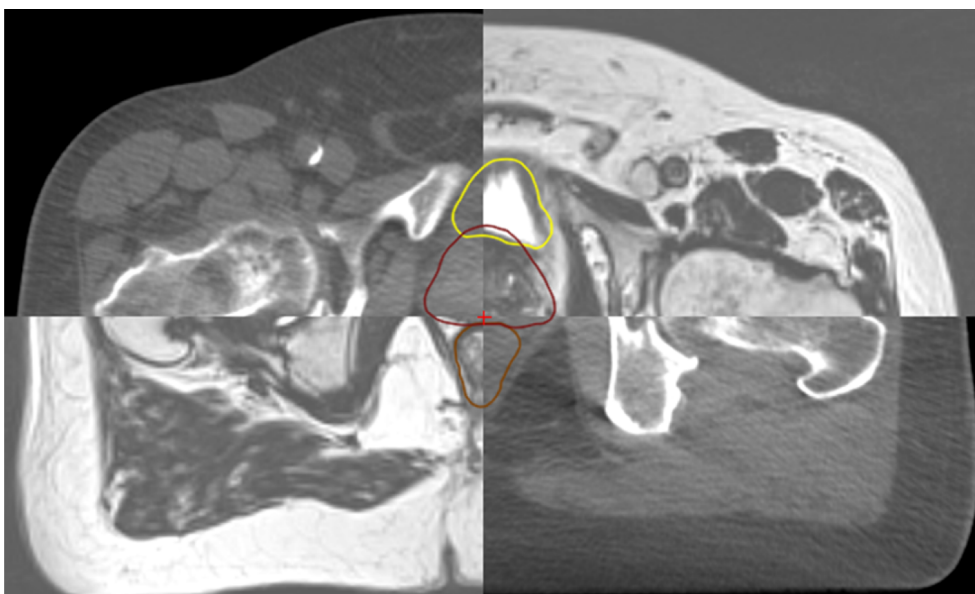
Fig. 1. Example MR-CBCT match in Aria with the PTV (red), bladder (yellow) and rectum (brown) planning structures shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
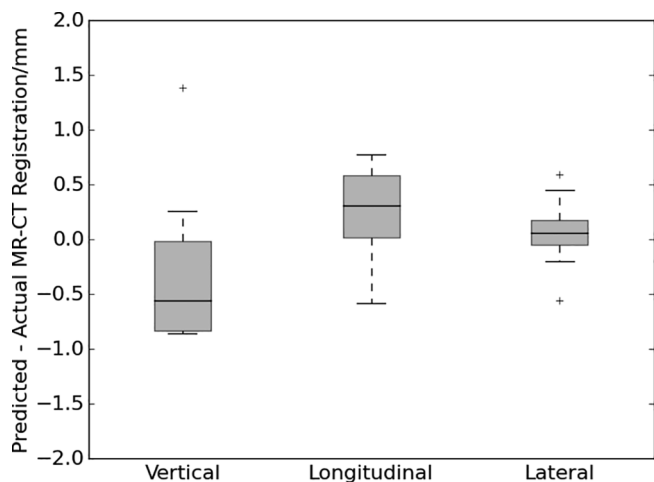

Fig. 2. Box plot of differences between predicted and actual MR-CT registration for the commutation assessment (patient cohort 1). There does appear to be a larger spread and a systematic offset in the vertical direction compared to the other two.

In addition, Aria will only accept non-CT additional reference data sets and so the CT was relabelled as an 'MR' by changing the DICOM tags Modality, SOPClassUID, ScanningSequence and SequenceVariant to 'MR', '1.2.840.10008.5.1.4.1.1.4', 'RM' and 'NONE' respectively. The same four radiographers independently matched the first fraction CBCT to the MR and to the CT as for cohort two.

The inter-observer variability of MR-CBCT and CT-CBCT soft-tissue matching was assessed with combined data from cohorts two and three. It was measured using an extension of the Bland-Altman method for multiple observers [15]. The difference between each observer's match and the mean of all observers match was plotted as a function of the mean of all observers match. Limits of Agreement (LoA) were estimated using the methodology detailed in Ref. [15] and give an assessment of the disagreement of the observers with the mean of all observers. The inter-observer error was also calculated as the standard deviation of the shifts across all four observers for each patient [16].

Table 1
The mean ± standard error of the mean (minimum, maximum) difference between MR-CBCT and CT-CBCT match (MR – CT). Cohort two patients were planned and treated using CT and matched with images correctly labelled. Cohort three patients were planned and treated using MR-only and matched with images which were DICOM relabelled (MR to 'CT' and CT to 'MR') to enable the MR to be the primary reference image.

| Match Type	Axis	Mean MR-CBCT and CT-CBCT Difference/mm	
		Cohort Two	Cohort Three
Automatic	Vertical	− 0.2 ± 0.2 (−1.7, 1.5)	− 0.6 ± 0.3 (−2.6, 1.8)
	Longitudinal	− 0.5 ± 0.2 (−2.7, 1.0)	0.7 ± 0.3 (−1.4, 2.4)
	Lateral	− 0.1 ± 0.2 (−1.7, 1.2)	− 0.3 ± 0.2 (−1.4, 1.0)
	All	− 0.3 ± 0.1 (−2.7, 1.5)	− 0.1 ± 0.2 (−2.6, 2.4)
Soft-Tissue	Vertical	− 0.1 ± 0.3 (−2.7, 1.8)	− 0.1 ± 0.3 (−3.3, 3.0)
	Longitudinal	− 0.2 ± 0.3 (−2.2, 1.9)	− 0.2 ± 0.5 (−7.9, 2.4)
	Lateral	− 0.1 ± 0.2 (−1.7, 1.2)	− 0.1 ± 0.2 (−1.6, 1.0)
	All	− 0.1 ± 0.1 (−2.7, 1.9)	− 0.1 ± 0.2 (−7.9, 3.0)

3. Results

### 3.1. Commutation assessment (Cohort One)

The differences between predicted and actual registration matrix are shown in Fig. 2. The mean difference in the vertical direction was $\Delta R_{Vert} = -0.7 \pm 0.4 \, (-3.2, 1.4)$ mm (± standard error of the mean (minimum, maximum)). The mean differences in the longitudinal and lateral directions were smaller, $\Delta R_{Long} = 0.3 \pm 0.1 \, (-0.6, 0.8)$ and $\Delta R_{Lat} = 0.1 \pm 0.1 \, (-0.6, 0.6)$, and across all directions was $\Delta R_{All} = -0.1 \pm 0.2$ mm.

3.2. Radiographer matching assessment (Cohorts Two and Three)

The mean difference in MR-CBCT and CT-CBCT automatic match was ⩽ 0.7 mm over all directions and for the soft-tissue match ⩽ 0.2 mm (see Table 1). All the soft-tissue match differences were within ± 3.3 mm except for one outlier in the longitudinal direction (see Fig. 3). The CT plan and MR-only plan cohorts had similar spread of
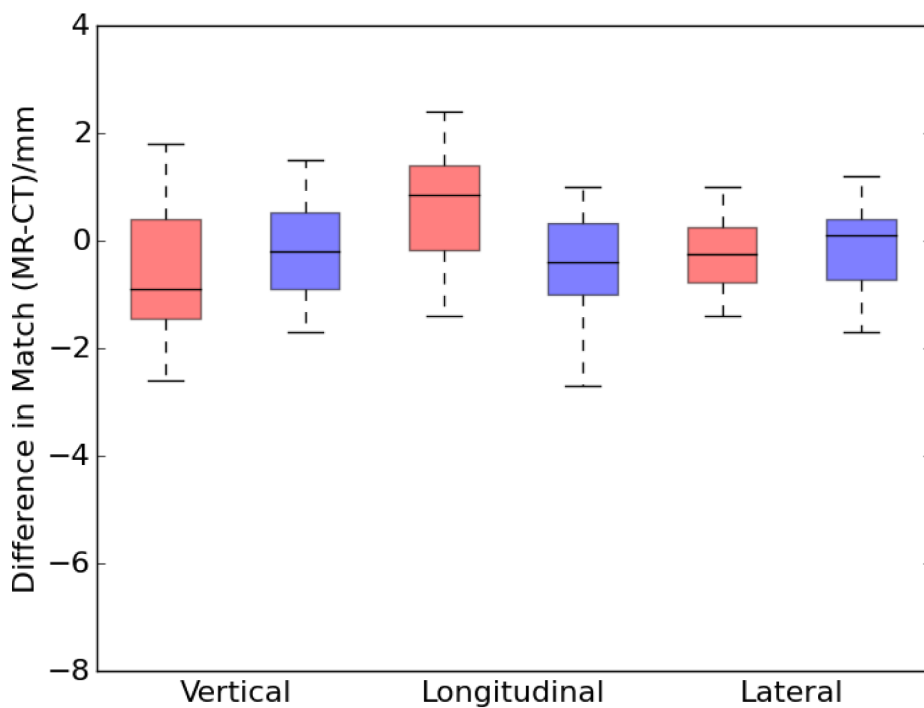
(a) Automatic Match
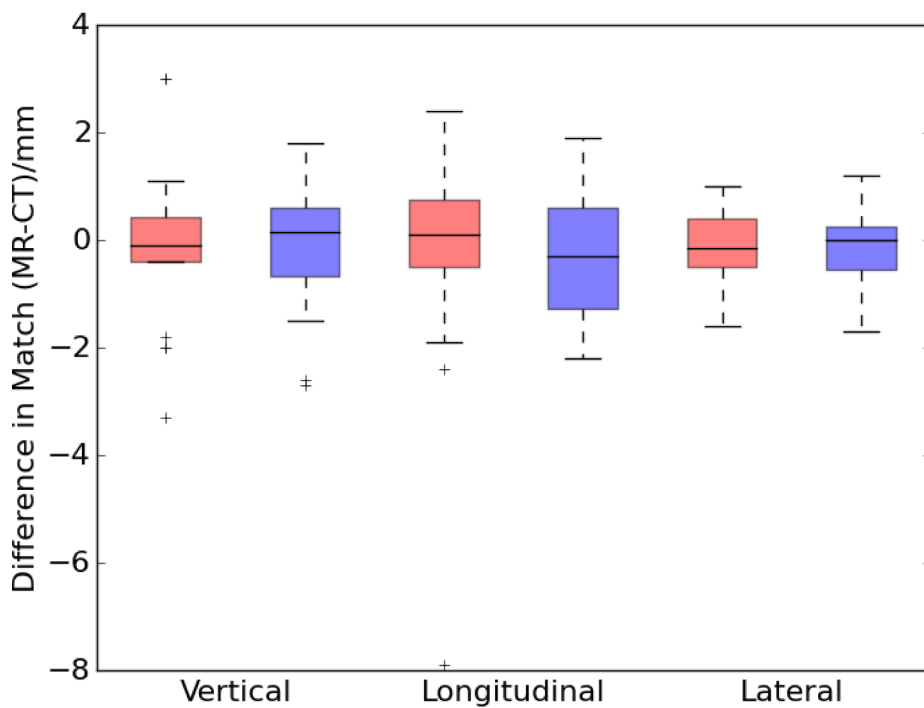
(b) Soft-Tissue Match

Fig. 3. Box plots of the difference between MR-CBCT and CT-CBCT (MR-CT) automatic (top) and soft-tissue (bottom) matches. CT-based plan patients (cohort two) are shown in blue and MR-only plan patients (cohort three) in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

MR-CBCT and CT-CBCT differences in the automatic match.

There appeared to be more inter-observer variability (Fig. 4) in the vertical direction for both CT-CBCT and MR-CBCT soft-tissue matches, with LoA being 3.0 mm and 3.5 mm for CT-CBCT and MR-CBCT matches respectively. In the other two directions the inter-observer variability was smaller, with the respective CT-CBCT and MR-CBCT LoA being

1.9 mm and 2.4 mm for the longitudinal direction and 0.5 mm and 0.9 mm for the lateral. The automatic matches showed similar inter-observer variability in all three directions, [0.9, 1.1, 0.6] mm (vertical, longitudinal, lateral) for the CT-CBCT matches and [1.4, 1.4, 0.9] mm for the MR-CBCT matches. There was $\leqslant 0.5$ mm difference between the CT-CBCT and MR-CBCT LoA in any direction in either the automatic or
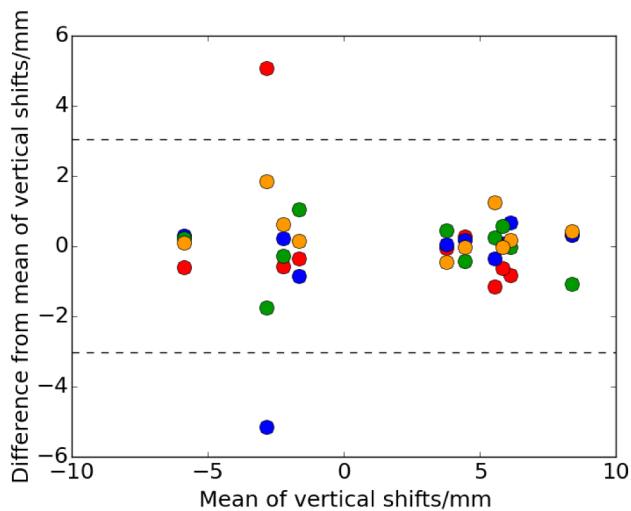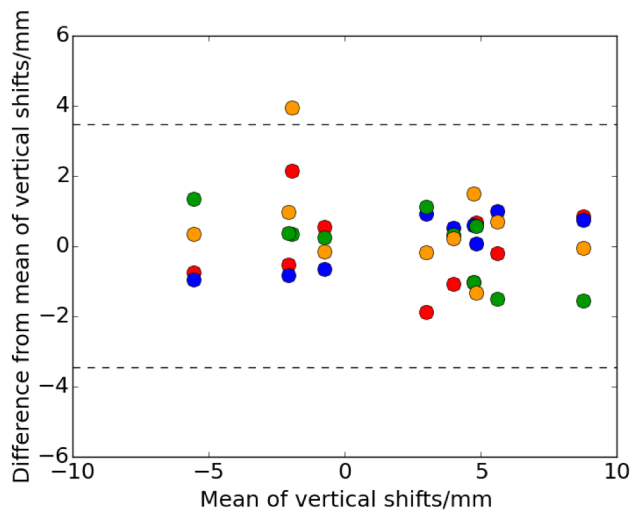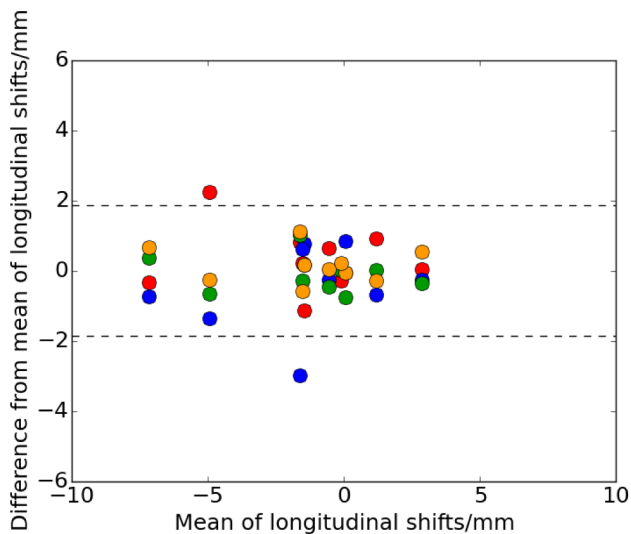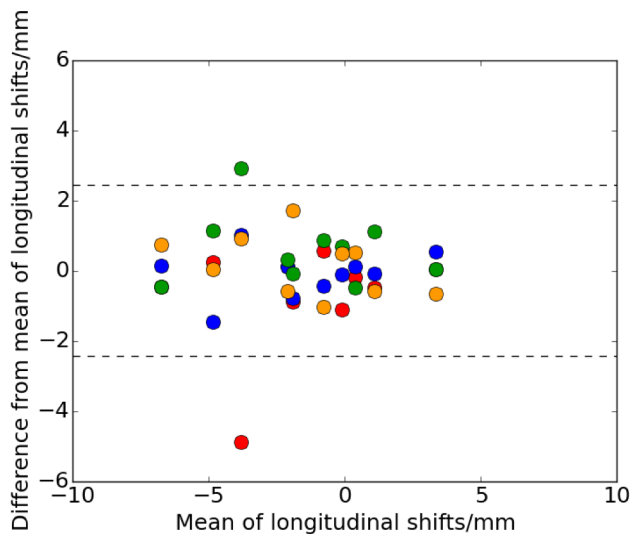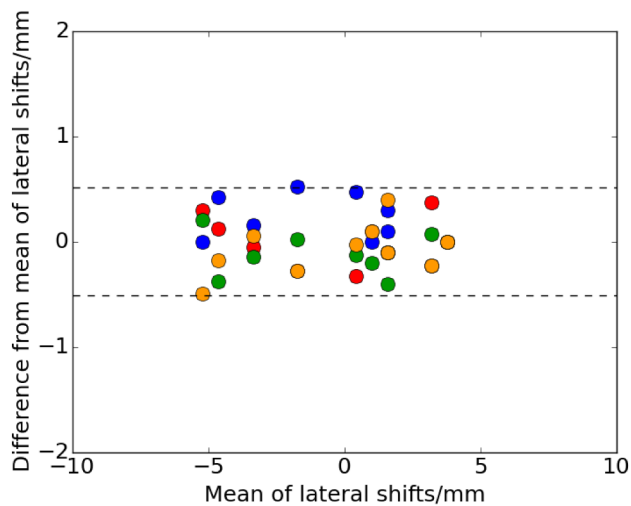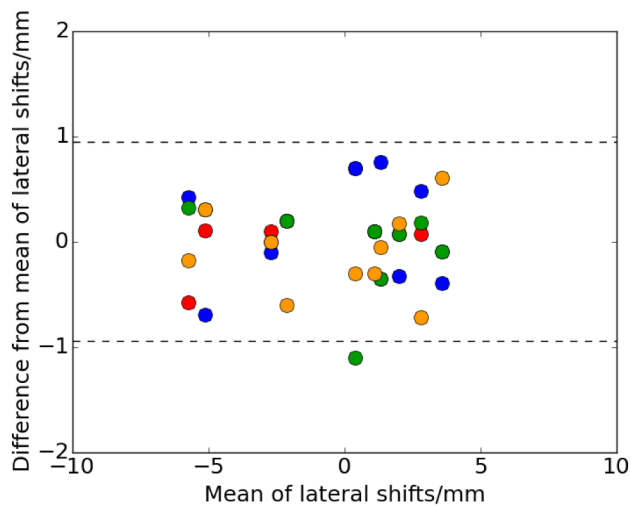
Fig. 4. The modified Bland-Altman plots showing the difference in match for each observer compared to the mean of all observers as a function of the mean of all observers. The blue, red, green and yellow circles indicate radiographers one, two, three and four respectively. The dashed lines show the Limits of Agreement (LoA). The CT-CBCT inter-observer variability is shown on the left-hand plots and the MR-CBCT variability on the right-hand plots for the vertical (top), longitudinal (middle) and lateral (bottom) directions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
The mean ± standard deviation of the interoberserver error (standard deviation of shifts across all observers) for the MR-CBCT and CT-CBCT matches. Data was combined for cohorts two and three.

Match Type	Axis	Mean Inter-Observer Error/mm	
		MR-CBCT	CT-CBCT
Automatic	Vertical	0.6 ± 0.3	0.4 ± 0.2
	Longitudinal	0.7 ± 0.2	0.5 ± 0.2
	Lateral	0.4 ± 0.2	0.3 ± 0.2
Soft-Tissue	Vertical	1.4 ± 1.2	1.0 ± 1.2
	Longitudinal	1.0 ± 0.9	0.8 ± 0.6
	Lateral	0.4 ± 0.2	0.3 ± 0.1

soft-tissue matches. The inter-observer error (Table 2) displayed similar results, with the vertical direction showing more variability for both MR-CBCT and CT-CBCT soft-tissue matches and the automatic matches being similarly variable in all directions. Again there was very little difference ($\leqslant$ 0.4 mm) between the inter-observer error for MR-CBCT and CT-CBCT.

4. Discussion

This study has evaluated the accuracy of CBCT soft-tissue matching using an MR as the reference image for MR-only prostate radiotherapy. The differences between MR-CBCT and CT-CBCT matching were small, with the mean differences for both automatic and soft-tissue matching being $\leqslant$ 0.7 mm in all directions. The mean soft-tissue matching difference was $\leqslant$ 0.2 mm, which is substantially less than the CT-CBCT soft-tissue matching inter-observer variability reported in this study of [3.0, 1.9, 0.5] mm (vertical, longitudinal, lateral). All except one difference in soft-tissue match was $\leqslant$ 3.3 mm. The patient with a larger difference had substantially different rectal filling in the CBCT compared to the MR despite undergoing identical bowel preparation, which may explain this outlier result. This suggests that MR-CBCT soft-tissue matching is as accurate as CT-CBCT soft-tissue matching for prostate radiotherapy.

Currently both Elekta and Varian linear accelerator manufacturers require the primary reference image, which is the only image available for on-line image matching, to be a CT. Therefore to be able to implement MR-CBCT matching as part of a MR-only radiotherapy process, it is necessary to relabel the MR as a DICOM 'CT'. This appeared to have no impact on the performance of the automatic image registration algorithm in Aria, with the distribution of the differences being similar between cohorts two and three (see Fig. 3). There appeared to be a slight difference in the longitudinal direction (cohort two $-$ 0.5 mm versus cohort three 0.7 mm), however the mean differences still agreed within the longitudinal inter-observer variability for the automatic CT-CBCT matches (LoA 1.1 mm), suggesting that this was not clinically significant.

This study has assessed the accuracy of MR-CBCT matching by using the CT-CBCT match as the gold standard. This was reasonable as CT-CBCT matching is the current clinical standard but it does have some potential limitations. The first issue is that differences in MR-CBCT and CT-CBCT match for the same patient depend on the quality of the MR-CT registration. If the internal anatomy was substantially different between the MR and CT (eg large differences in bladder filling), this could have resulted in a sub-optimal MR-CT registration and therefore a difference in the CT-CBCT and MR-CBCT matches, causing an over-estimation of the MR-CBCT uncertainty for that patient. Over a patient population the MR-CT registration errors will tend to push the mean difference in MR-CBCT and CT-CBCT matches to zero but broaden the standard deviation of these differences. This issue was attempted to be controlled for by focusing the MR-CT registration on the prostate-only PTV, since the prostate position is relatively insensitive to differences in

bladder filling [17]. In this study the very small standard errors of the mean ($\leqslant$ 0.5 mm) suggest that MR-CT registration errors did not cause an under-estimation of the MR-CBCT uncertainty.

The second related issue is the structure set used by the radiographers in assessing the soft-tissue match. In order to ensure an accurate comparison between the MR-CBCT and CT-CBCT match, the same structure set was used for both matches (CT-based structures for cohort two and MR-based structures for cohort three). Again, if there were differences in the internal anatomy between the MR and the CT, this would have resulted in a discrepancy on one of the images between the reference image data and the outlined structure. This was controlled by using two cohorts, one with CT-based structures and the other with MR-based structures to assess if there was a systematic difference between the two. The common structure set may explain why the mean differences in soft-tissue matches (where the radiographers used the structures) were smaller than the automatic matches.

The final issue is the poorer soft-tissue contrast of CT compared to MR. A priori this would suggest that radiographers would find soft-tissue matching using MR easier and more accurate than with CT, and therefore differences between MR-CBCT and CT-CBCT matches may be due to the MR-CBCT match being closer to the ground truth [9]. This issue is very hard to control for and is a limitation of this study. However, the small mean differences indicate that MR-CBCT soft-tissue matching is at least as accurate as CT-CBCT.

The results in this study compare well with the two other studies investigating MR-CBCT matching. Doemer et al. used a manual MR-CBCT registration which was compared to the clinical CT-CBCT registration and found mean differences of [$-$ 1.5 ± 2.5, 0.7 ± 1.9, $-$0.1 ± 1.4]mm (vertical,longitudinal,lateral) [11]. Korhonen et al. used an automatic registration focused on a 10 cm cube in the centre of the images [9]. They reported mean differences to CT-CBCT match of [1.5 ± 0.6, 0.7 ± 0.7, $-$0.5 ± 1.2]mm (vertical,longitudinal,lateral). The mean differences found in this study were similar in the longitudinal and lateral directions and smaller in the vertical direction (see Table 1). This corroborates the finding of this study that MR-CBCT soft-tissue matching is not significantly different to CT-CBCT matching.

The inter-observer variability was very similar between CT-CBCT and MR-CBCT registrations, with LoA and inter-observer errors being within 0.5 mm for each direction. The vertical direction showed more inter-observer variability for the soft-tissue matches than the other directions, which was true for both CT-CBCT and MR-CBCT matches (see Fig. 4). Manual soft-tissue matching involves balancing the coverage of the prostate and the seminal vesicles. If the seminal vesicles on the CBCT are shifted compared to the reference image, this balance will involve clinical judgement which is likely to increase inter-observer variability, primarily in the vertical direction. To authors' knowledge, MR-CBCT inter-observer variability for prostate matching has not been reported previously in the literature. McNair et al. investigated the inter-observer variability of CT-CBCT soft-tissue matching and reported mean inter-observer error of 1.6 ± 0.7 mm, 1.4 ± 0.9 mm and 0.4 ± 0.3 mm (± standard deviation) for the vertical, longitudinal and lateral directions repectively [16]. This agrees well with the results found in this study with both the CT-CBCT and MR-CBCT inter-observer errors being lower but within one standard deviation of those values (see Table 2). McNair et al. also found that the inter-observer variability in the vertical direction was the largest, suggesting it is not specific to MR-CBCT matching but due to patient anatomy differences.

MR imaging has the ability to generate many different image contrasts, which could have an impact on the accuracy of MR-CBCT matching. This study has only evaluated T2-weighted MR images and so would not directly apply to MR images with substantially different image contrast.

In conclusion, CBCT soft-tissue matching by experienced therapy radiographers using an MR as the reference image appears not to be clinically significantly different to using CT, with differences being less

than inter-observer variability. Relabelling the MR as a 'CT' in the DICOM header does not affect the performance of the automatic registration algorithm. This suggests using a MR for soft-tissue matching within a MR-only workflow is feasible and accurate. This will enable an MR-only workflow to be implemented at centres where prostate fiducial markers are not routinely used and enable the extension of MR-only radiotherapy to other clinical sites.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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