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Verification imaging in prostate MR-only radiotherapy: Are fiducial markers necessary?

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ABSTRACT

Purpose/objective: MR-only radiotherapy planning exploits the benefits of MRI soft-tissue delineation, whilst negating the registration inaccuracies caused by MRI CT fusion. Fiducial markers have conventionally been used in prostate radiotherapy to reduce on-treatment image matching variability. However, this is an invasive procedure for the patient, and presents technical difficulties in an MR-only pathway as fiducial markers are difficult to visualise on MRI. This study compares MR-CBCT soft-tissue matching to fiducial matching in an MR-only prostate pathway.

Material/methods: Four therapeutic radiographers reviewed first fraction CBCTs for 25 patients. The CBCT was compared to the planning MRI, a T2 weighted sequence for the soft-tissue match and compared to a T1 weighted MRI sequence for the fiducial match. Inter-observer variability was quantified using the inter-observer error and 95 % limits of agreement from a modified Bland-Altman analysis. Accuracy of the soft-tissue match was quantified by calculating the difference from the fiducial match.

Results: Limits of agreement on the MR soft-tissue match were 1.5 mm, 4.0 mm, 3.5 mm and fiducial match 2.5 mm, 3.6 mm, 2.5 mm (lateral, longitudinal, vertical). Inter-observer error (±standard deviation) on the MR soft-tissue match were 0.6(±0.5) mm, 1.8(±1.1) mm, 1.7(±0.7) mm and fiducial match 0.7(±1.1) mm, 1.1(±1.5) mm, 0.8(±0.7) mm (lateral, longitudinal, vertical). The difference of the soft-tissue match from the fiducial match was 0.3(±1.1) mm, −0.1(±2.7) mm, 0.1(±1.9) mm (lateral, longitudinal, vertical).

Conclusion: MR-CBCT soft-tissue matching has similar accuracy and inter-observer variability as fiducial matching. This suggests fiducial markers are not necessary in an MR-only prostate radiotherapy pathway.

Implications for practice: MR-only prostate radiotherapy does not require fiducial markers since MR-CBCT soft tissue matching can be used for IGRT.

Introduction

The use of Magnetic Resonance imaging (MRI) in prostate radiotherapy planning for enhanced soft-tissue visualisation is well established. A planning MRI is often used alongside planning computed tomography (CT) to exploit the benefits of soft-tissue imaging whilst using CT scan Hounsfield units[1] for dosimetric planning. However, there are registration inaccuracies in fusing the planning CT and planning MRI scan together.[2] These can be caused from differences in patient positioning or differences in bladder and rectal filling between scans.[2] An MR-only pathway negates the requirement of a CT scan by creating a synthetic CT generated from the MRI to provide density data to enable dosimetric planning.[3]

One form of image guided radiotherapy (IGRT) is the use of X-ray imaging acquired on the treatment machine with the patient in the treatment position immediately before treatment to verify target position. IGRT has facilitated the introduction of smaller PTV margins improving organ at risk (OAR) sparing without impacting tumour control.[4] In prostate radiotherapy, two main on-treatment IGRT methods are used[5,6]: soft-tissue matching cone-beam CT (CBCT), or fiducial matching, with either CBCT or 2D kV pairs. Soft-tissue matching enables the therapeutic radiographer (observer) to match the prostate and seminal vesicles target, and then assess the OAR position. OARs such as the bladder and rectum can change size and position due to changes in filling on a daily basis, despite

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attempts to minimise this by most radiotherapy departments through using bladder and rectal preparation protocols.[6] The variation in OAR size and shape impacts the prostate and seminal vesicles position, making target verification essential.

Fiducial marker matching has reduced inter-observer variability due to the increased automation, but does remove the ability to shift to ensure dose coverage of the seminal vesicles in the case of differences in bladder or rectal filling with 2D kV pairs. There is evidence that there is less inter-observer variability with a fiducial match than soft-tissue matching, and therefore the assumption is that this is more accurate.[7] However, the benefits of seminal vesicle position and OAR assessment are limited in the fiducial marker match pathway.

Additionally, fiducial marker insertion is an invasive procedure and the risks associated with fiducial marker have been widely reported[5]; Loh et al. (2015)[8] report an infection rate of 7.7 %, and 2.8 % of patients being hospitalised despite using prophylactic antibiotics. Therefore, if soft-tissue matching is an accurate alternative to fiducial marker matching, then this would provide an appealing solution to fiducial marker insertion and could account for why 66 % of UK centres already use soft-tissue matching[6] in a conventional prostate radiotherapy pathway.

Clinical implementation of prostate MR-only radiotherapy has mainly relied on fiducial markers for on-treatment IGRT,[9–11] with only one centre reporting the use of online soft-tissue matching MR-CBCT IGRT.[12] However, the identification of the fiducial marker in an MR-only pathway is difficult in both automatic and manual registrations[13,14] and Maspero et al. (2018)[13] concluded that the risk of mislocation of patient positioning is still too high to solely rely on fiducial marker for IGRT verification. Tyagi et al. (2020)[15] report 4.1 % of patients required a CT scan since the fiducial marker could not be identified on the planning MRI.

In previously published work by our group, soft-tissue matching can be sufficiently accurate to be used in an MR-only workflow[16,17] with Brooks et al. (2021)[17] demonstrating that MR-CBCT matching was at least as accurate as CT-CBCT soft-tissue matching. This provides a solution to the challenge of fiducial marker visualisation in an MR-only pathway for IGRT verification.

However, a head-to-head comparison between fiducial marker matching and soft-tissue matching for MR-only radiotherapy in early-stage prostate cancer has not been performed. If soft-tissue matching has a similar accuracy and inter-observer variability as fiducial marker matching, then soft-tissue matching can be used with the same PTV margins to provide high quality radiotherapy without an additional invasive procedure for the patient. This paper aims to investigate whether MR-CBCT soft-tissue matching has the same accuracy and variability as fiducial matching and thus whether fiducial markers are unnecessary.

Methods

Observers

Four therapeutic radiographers with MR prostate CBCT soft-tissue matching experience at the Northern Centre for Cancer Care, Newcastle upon Tyne, UK reviewed first fraction CBCTs for 25 patients.

Image acquisition

Image data was acquired between April 2017 and April 2019 at the Radiation Oncology Department, Calvary Mater Hospital, Newcastle, New South Wales, Australia where fiducial markers are routinely used in prostate radiotherapy. The CBCT was compared to the planning MRI scan; a T2 weighted sequence for the soft-tissue match, and the CBCT was compared to a T1 weighted MRI sequence for the fiducial match. The MRI sequences were acquired in a single session on a Siemens Skyra 3T (Siemens Healthineers, Erlangen, Germany), equipped with DORADOnova MR3T laser bridge (LAP GmbH Laser Applikationen, Lüneburg, Germany) for alignment and Q-Fix indexable flat couch top (CQ Medical, Avondale, PA) with a 1×18-channel body coil anteriorly and spine coil posteriorly. The T2 sequence was isotropic transverse fast spin echo T2 SPACE voxel size is 1.7mmx1.7mmx1.6 mm TR1200, TE103. The T1 was a transverse gradient echo voxel sixe $0.7 \times 0.7 \times 2.0$ mm, TR 689, TE 6.66, flip angle 80°.

Patient data

Twenty-five patients aged 58–83 with a pre-treatment PSA range 0.88–33.8 were recruited to the study. The patients were immobilised using Medtec kneefix and anklestocks (CQ Medical, Avondale, PA) at the planning scan and each treatment. Bowel preparation consisted of patients having a one-week benefibre dietary supplement and asked to attempt a bowel motion before the planning scan and each treatment. Bladder preparation consisted of the patients emptying their bladder and drinking 500 ml of water 30 min before each planning scan and treatment. Patients were treated with 60Gy in 20 fractions on a Varian Clinac iX (Varian Medical Systems, Palo Alto, CA) with CBCT full arc acquisition, half fan filter, 125 kV, 80 mA, 13 ms, small focal spot, 45 cm diameter field of view and 512×512 image matrix, 2.5 mm slice. The study was ethically approved by the Hunter New England Human Research Ethics Committee (HREC Registration No: 16/07/20/3.01, NSW HREC Reference No: HREC/16/HNE/298, Australian New Zealand Clinical Trials Registry ACTRN12616001653459) and informed consent was obtained from all patients. All patient data was anonymised prior to inclusion in this retrospective review. Patients with hip prosthesis and metallic implants were excluded from the study.

Image matching

CBCT image matches were conducted in RayStation (RaySearch Laboratories, Stockholm, Sweden), an independent treatment planning system. (The independent planning platform allowed anonymised patient data to be imported from a different radiotherapy centre without the requirement of specific machine set-up data). The CBCT image matches were conducted in the "image registration" module. This uses a mutual information rigid registration algorithm that simulates the clinical matching process. After the initial registration, the observer would match the prostate gland on the CBCT to the T2 weighted MRI with consideration of seminal vesicle coverage and organ at risk position affected by variations in bladder and rectal filling. The translational shifts were then recorded. Fiducial markers were not visible on T2 MR sequence and therapeutic radiographers performed the soft-tissue match first, ensuring the fiducial marker match did not influence the soft-tissue match. The observers then conducted the fiducial match by identifying each fiducial marker as a structure on the CBCT and then running a "point of interest" image match algorithm to the fiducial marker planning structure on the T1 weighted MRI. The image match translations were then recorded.

Statistical analysis

Inter-observer variability was quantified using the inter-observer error (mean of the per-patient standard deviation in therapeutic radiographer matches) and 95 % limits of agreement from a modified Bland-Altman analysis[17,18] in Microsoft Excel. Accuracy of the soft-tissue match was quantified by calculating the difference from the fiducial match (see Fig. 1).

Table 1
Shows the percentage agreement of the soft-tissue match to the fiducial marker match.

	Lateral	Longitudinal	Vertical
+/− 2 mm	92 %	52 %	64 %
+/− 3 mm	100 %	76 %	88 %
+/− 4 mm	100 %	92 %	96 %

Results

The mean difference of the soft-tissue match from the fiducial match was 0.3(±1.1) mm lateral, −0.1(±2.7) mm longitudinal and, 0.1(±1.9) mm vertical (±standard deviation). The percentage of soft-tissue matches that were within fiducial match limits of agreement were 96 % lateral, 84 % longitudinal, 76 % vertical direction. Only 6 patients (24 %) had differences >3 mm and only 1 patient (4 %) had a difference >5 mm (see Table 1 and Fig. 2).

Table 2 shows the inter-observer error and the limits of agreement in the soft-tissue match and the fiducial marker match. Overall, the largest difference between the soft-tissue match and the fiducial match limits of agreement and inter-observer error was 1 mm. The direction with the most variation in inter-observer error and limits of agreement was the longitudinal direction, with a maximum limit of agreement of 4 mm, however, the extent of the variation between observers was similar (within 0.4 mm) in both the soft-tissue match and fiducial match.

Figs. 3–5 show the observers agreement, the mean shifts in both longitudinal and vertical directions are up to 100 mm. This is because the planning scan and the CBCT were not registered at data import, therefore there are large shifts that would not be seen in the clinical setting. However, the difference from the mean of the shifts shows the agreement among the observers which is the aim of this study.

Discussion

This study assessed the differences in MR-CBCT soft-tissue matching and fiducial marker image matching in an MR-only prostate pathway. Soft-tissue matching appeared accurate, with mean shifts ≤0.3 mm different to fiducial matching. Inter-observer variability was also very similar between the two image matching techniques, and limits of agreement were within 1 mm of each other for each direction. This suggests either method of image matching is acceptable in the clinical setting.

A direct comparison of soft-tissue matching and fiducial matching has not been published in an MR-only pathway. However, the differences between soft-tissue and fiducial matching in this study are similar to those reported in CT-only pathways. Tanabe et al. (2019)[19] reported differences of 0.3 mm, 0.0 mm, 0.7 mm (lateral, longitudinal, vertical)., similar to the 0.3 mm, −0.1 mm, and 0.1 mm in this study. Tanabe et al. (2019)[19] report 97 %, 50 % and 41 % (lateral, longitudinal, vertical) of the soft-tissue matches were within 2 mm of the fiducial match. Oehler et al. (2014)[20] found that differences between fiducial and soft-tissue match were within 2 mm for 96 %, 79 %, 86 % of matches (lateral, longitudinal, vertical). We found similar agreement within 2 mm in the lateral (92 %), and slightly higher agreement in the longitudinal (52 %) and vertical (64 %) as Tanabe et al. (2019),[19] although lower rates of agreement than Oehler et al. (2019).[20] Tanabe et al. (2019)[19] reported 100 %, 99 % and 97 % of the soft-tissue matches were within 3 mm of the fiducial match. A similar study by Barney et al. (2011)[7] gave agreements of 87 %, 49 % and 41 %. The results of our study sit between those two, with 100 %, 76 % and 88 % (lateral, longitudinal, vertical) of soft-tissue matches within 3 mm of the fiducial match. All but one patient soft-tissue match agreed within 5 mm with the fiducial marker match. This implies that soft-tissue matching is as accurate as fiducial marker matching. There were larger differences in the longitudinal and vertical direction than the lateral. This may be because shifts in the seminal vesicle position relative to the prostate due to changes in bladder and rectal filling tend to move in those directions. This suggests that some of the differences in these directions were not due to inaccuracies in the soft-tissue match but because the soft-tissue match was accounting for changes within the internal anatomy that the fiducial marker match was not. Therefore, the accuracy of soft-tissue matching may be even greater than these results suggest.

The accuracy of MR-CBCT soft-tissue matching compared to CT-CBCT soft-tissue matching has been previously evaluated,[16] with ≤0.2 mm in all directions. The equivalence between CT-CBCT soft-tissue matching and fiducial marker matching and between CT-CBCT and MR-CBCT soft-tissue matching supports the results found in this study which suggests that MR-CBCT soft-tissue matching is equivalent to fiducial marker matching.

Interestingly, this study found that the inter-observer variability for the soft-tissue match was also very similar to the fiducial marker match. The differences in the limits of agreement were ≤0.4 mm in each direction, suggesting the inter-observer variability was equivalent. This was a surprising result since it was expected that the larger amount of clinical decision making involved in the soft-tissue matching would result in larger inter-observer variability.

The inter-observer variability of MR fiducial marker matching has not been previously evaluated in the literature. However, the

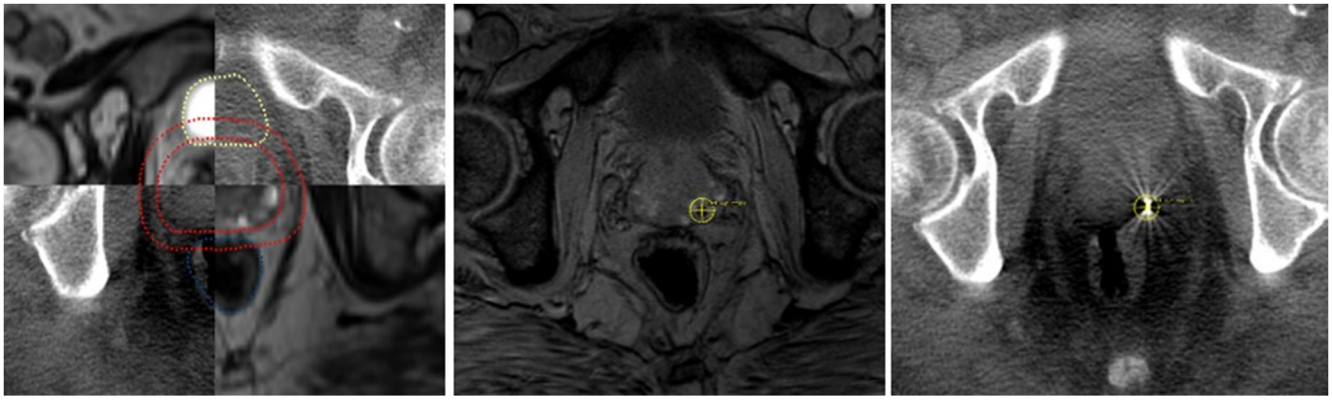


Figure 1. T2 weighted MRI and CBCT fusion for soft-tissue match (left). T1 weighted MRI with fiducial marker in yellow circle (centre). CBCT with fiducial marker identified in yellow circle for fiducial marker match (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

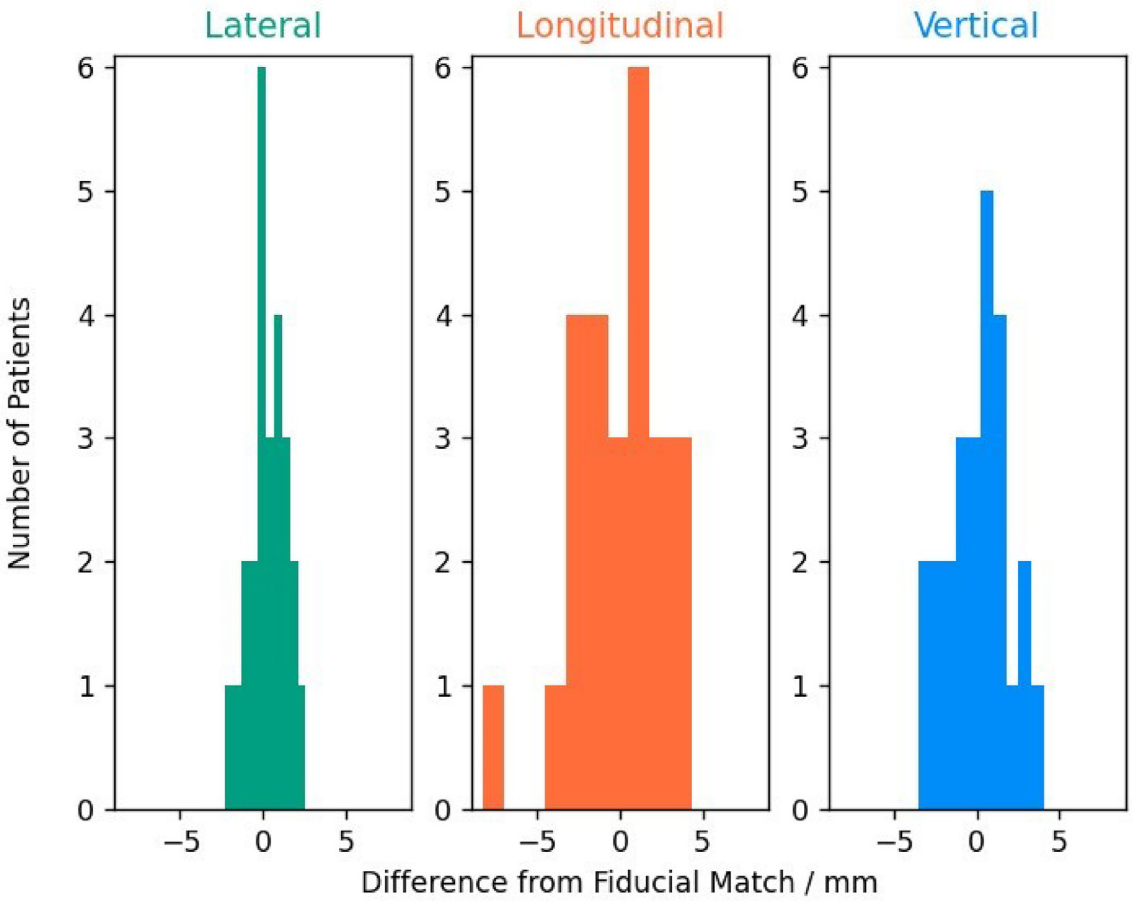


Figure 2. Histogram shows the difference of the soft-tissue match from the fiducial match of all patients.

Table 2
Shows the mean inter-observer error and mean limits of agreement in the soft-tissue match and the fiducial marker match.

(mm)	Soft-tissue match		Fiducial marker match	
	Inter-observer error (±standard deviation)	Limits of agreement	Inter-observer error (±standard deviation)	Limits of agreement
Lateral	0.6 (±0.5)	1.5	0.7 (±1.1)	2.5
Longitudinal	1.8 (±1.1)	4.0	1.1 (±1.5)	3.6
Vertical	1.7 (±0.7)	3.5	0.8 (±0.7)	2.5

variability in CT fiducial marker matching and MR-CBCT soft-tissue matching have. Wyatt et al. (2019)[16] reported prostate soft-tissue match MR-CBCT limits of agreement of 0.9 mm, 2.4 mm, 3.5 mm (lateral, longitudinal, vertical). Furthermore, Brooks et al. (2021)[17] demonstrated agreement in a large sample of 23 observers of MR-CBCT soft-tissue match of 1.1 mm, 2.4 mm, 2.6 mm (lateral, longitudinal, vertical) limits of agreement. These results are consistent with those found in this study, although with larger differences in the longitudinal direction (2.4 mm in the previous studies compared to 4.0 mm in this study.) This may be due to the larger CBCT slice thickness in this study 2.5 mm compared to 2 mm which could result in reduced CBCT image quality. The MR-CBCT soft-tissue matching inter-observer error was also similar (within 0.4 mm) of that reported for CT-CBCT soft-tissue matching.[21]

The inter-observer variability in CT fiducial marker and soft-tissue matching was evaluated by Deegan et al. (2015).[22] They reported limits of agreement for fiducial markers substantially less than for soft-tissue: fiducial match limits of agreement of 0.8 mm, 1.1 mm, 1.2 mm (lateral, longitudinal, vertical) and soft-tissue match limits of agreement 1.5 mm, 2.5 mm, 2.0 mm (lateral, longitudinal, vertical). The fiducial match limits of agreement in this study were 2.5 mm, 3.6 mm, 2.5 mm (lateral, longitudinal, vertical). This suggests that MR fiducial marker matching has greater inter-observer variability than CT fiducial marker matching.

O'Connor et al. (2023)[23] suggests that variation in the fiducial marker image match could be due to the poor visualisation of the fiducial marker on the MRI. In this study the T1 weighted MRI was used for the fiducial marker match, the fiducial markers were visible, but not as clearly as in a conventional CT pathway, which could explain the increased variation among observers compared to Deegan et al. (2015)[22] reported limits of agreement. Maspero et al. (2018)[13] also warned that the risk of fiducial marker mislocation in MR-only pathway means it cannot be relied upon for IGRT verification. This further demonstrates the relevance of using soft-tissue matching in an MR-only pathway.

McNair et al. (2015)[21] reported inter-observer error of prostate CT-CBCT soft-tissue matching of 0.4(±0.3) mm, 1.4(±0.9) mm and 1.6 (±0.7) mm (± standard deviation) (lateral, longitudinal, vertical). Our soft-tissue match findings of 0.6(±0.5) mm, 1.8(±1.1) mm, 1.7(±0.7) mm agree well with McNair et al. (2015).[21] Furthermore,

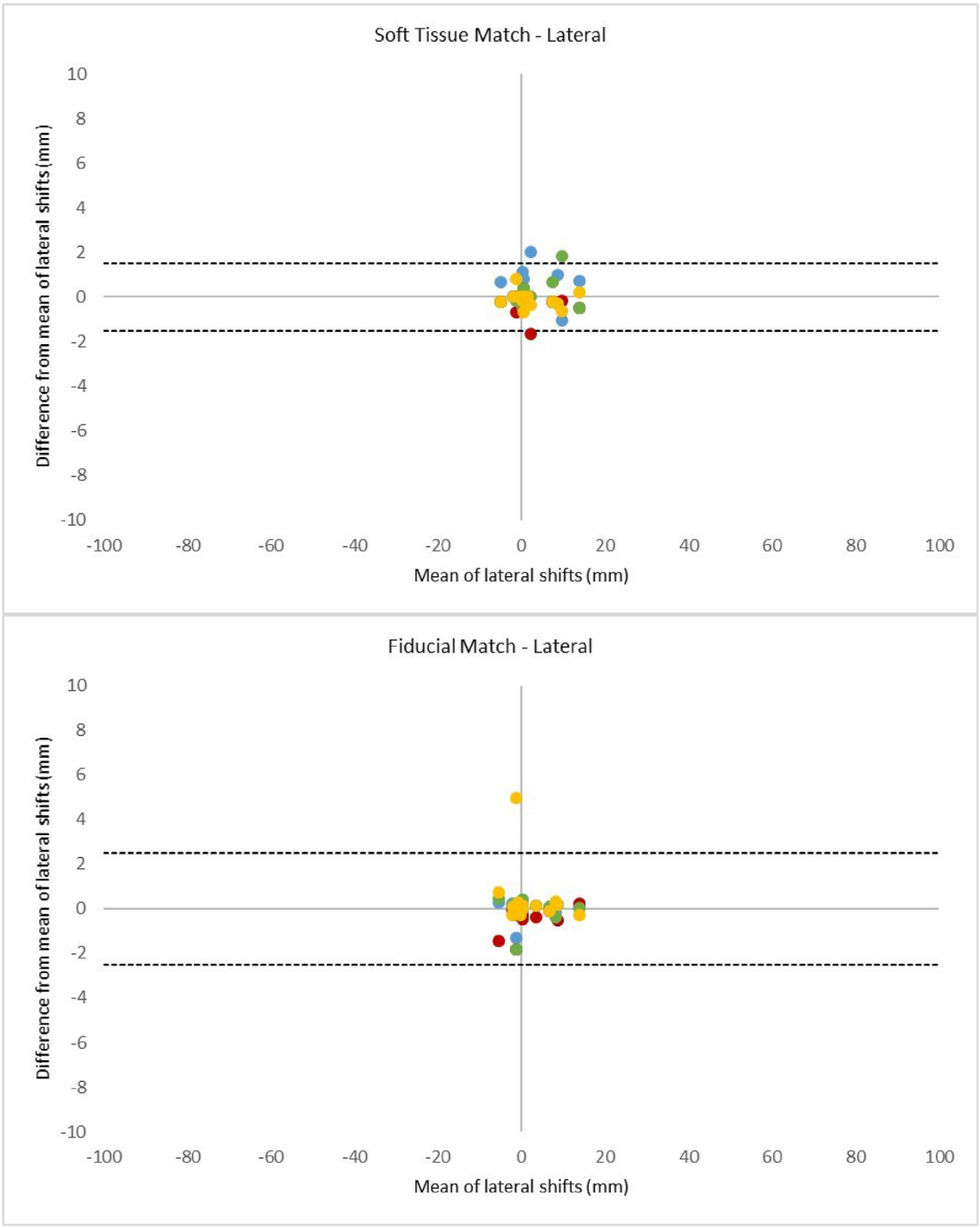


Figure 3. Modified Bland–Altman plots show lateral shifts of each therapeutic radiographer image match compared to the mean of all therapeutic radiographers (each therapeutic radiographer is represented as a different colour) in soft-tissue match and fiducial match. The dotted lines show the limits of agreement. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

our fiducial matches are also very similar at 0.7(±1.1) mm, 1.1(±1.5) mm, 0.8(±0.7) mm (lateral, longitudinal, vertical). These similar results were not expected since the perception of fiducial marker matching is that it is more reliable than soft-tissue matching.

One limitation of this study is that the observers were more experienced in soft-tissue matching than fiducial marker matching. However, the purpose of using fiducial markers is that the match is automatic and objective, and the observer's experience has very little impact on inter-observer variability. Therefore, the similarity between soft-tissue matching and fiducial matching was not expected. Previous studies of agreement in therapeutic radiographer soft-tissue matching have defined 5.0 mm as a clinically acceptable threshold.[24] Barney et al. (2011)[7] accepts up to the PTV margin, which is 4 mm in this context. The MR-CBCT limits of agreement were ≤4.0 mm in all directions, suggesting it meets this clinically acceptable threshold. McNair et al. (2015)[21] reported increased variation between observers in the vertical and longitudinal directions, and explained the longitudinal discrepancies are due to

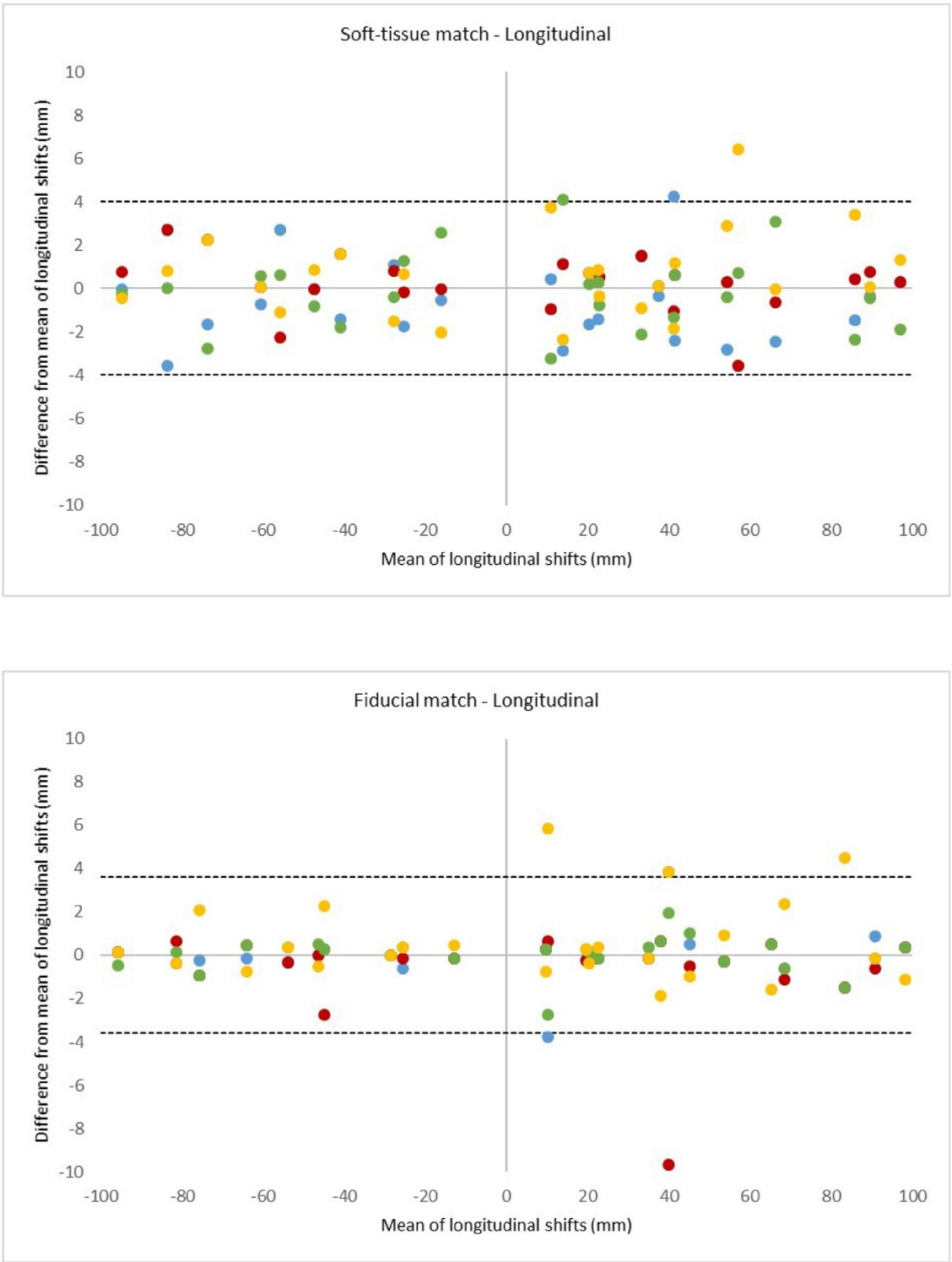
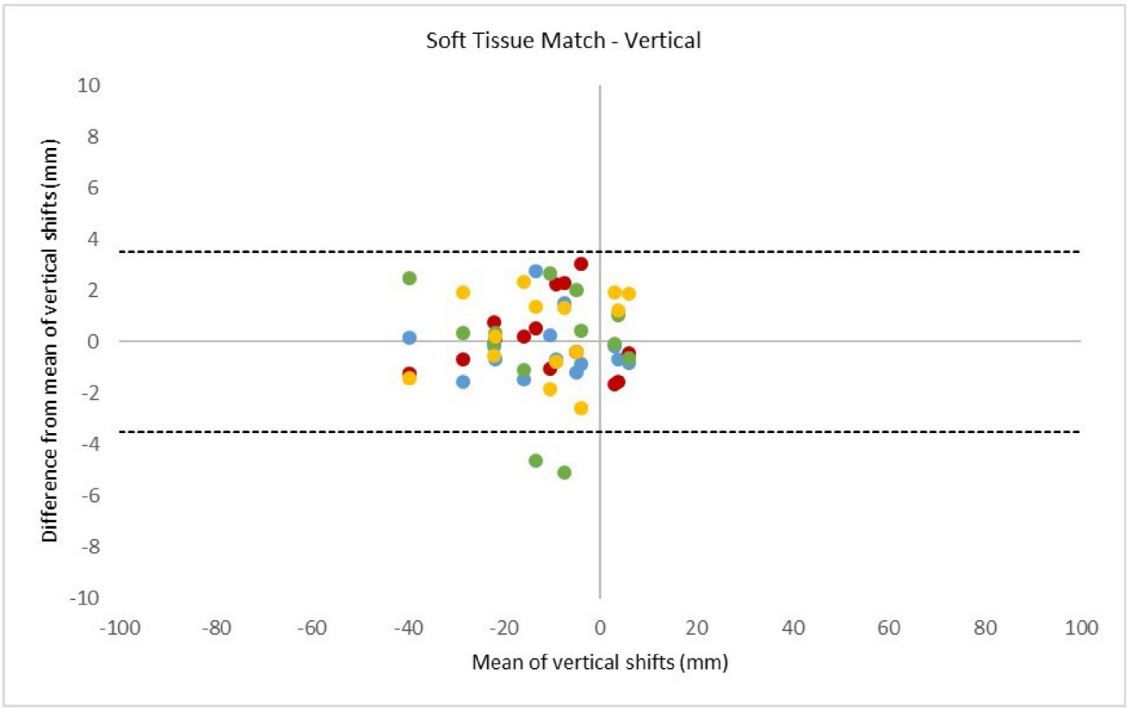


Figure 4. Modified Bland–Altman plots show longitudinal shifts of each therapeutic radiographer image match compared to the mean of all therapeutic radiographers (each therapeutic radiographer is represented as a different colour) in soft-tissue match and fiducial match. The dotted lines show the limits of agreement. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

difficulty visualising the prostate on the planning CT. Since there is good soft-tissue definition of the prostate on the planning MRI, in this study the difficulty is the visualisation of the prostate on the CBCT. An example of this is the anomaly in Fig. 2, the only patient with >5 mm difference between the fiducial match and soft-tissue match is in the longitudinal direction. In this patient, the CBCT had a ring artefact, causing the boundary between the bladder and prostate being difficult to see in the sagittal plane. This resulted in inter-observer variation of up to 10 mm in the soft-tissue match on this patient CBCT. The CBCTs in this study used an 800 mAs, whereas previous studies[16,17] used 900 mAs, which would contribute to better CBCT image quality and increased agreement among



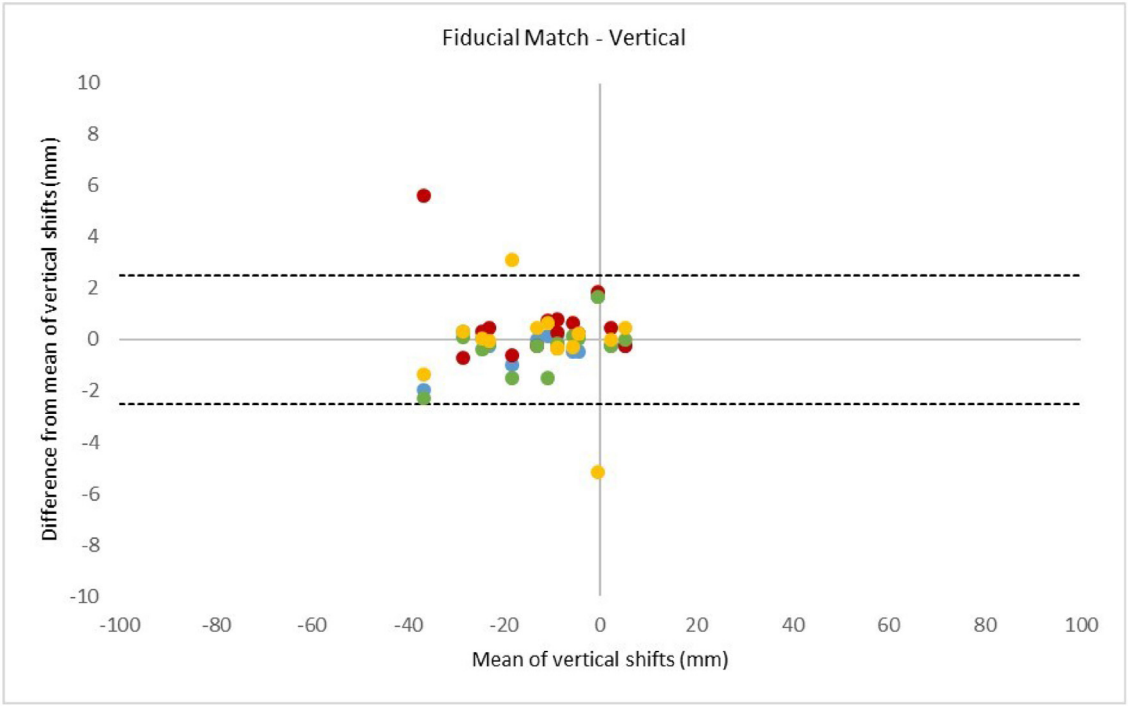


Figure 5. Modified Bland–Altman plots show vertical shifts of each therapeutic radiographer image match compared to the mean of all therapeutic radiographers (each therapeutic radiographer is represented as a different colour) in soft-tissue match and fiducial match. The dotted lines show the limits of agreement. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

observers. Furthermore, the fiducial markers were visible on the CBCT, which would cause artefact and affect the CBCT image quality for the soft-tissue match. The markers were not visible on the T2 weighted MRI, so there was no bias in the soft-tissue match, the T1 weighted MRI was acquired in the same session and was used for the fiducial match since the markers were visible in that sequence.

O'Connor et al. (2023)[23] compared MR-CBCT matching to CT-CBCT matching in prostate soft-tissue match and prostate fiducial marker match and reported limits of agreement of <0.5 mm in all directions for both prostate soft-tissue match and prostate fiducial match. However, a small sample of 5 patients were presented, and unlike this study, the soft-tissue match and fiducial marker match

were in different patients so no direct comparison could be made. One explanation for the limits of agreement being significantly smaller than previous studies[16,17] is that the image matches were conducted in Aria software that displayed the online clinical match position as zero. This could have caused bias in the observers as the matching software displayed the clinically accepted treatment position. In this study, an independent platform was used to remove this bias.

While fiducial matching is less time consuming than CBCT soft-tissue matching,[7,19] the local protocol states that all image matches are completed within 90 s and patients are treated within a standard 15-min appointment. The additional resource required for fiducial marker implantation and potential complications should also be considered in view of the small additional time burden of soft-tissue matching, particularly with hypo-fractionated treatment regimes becoming more common. Furthermore, Brooks et al. (2021)[17] reported that CT based prostate soft-tissue matching skills are transferrable to MR-CBCT matching, demonstrating that the training burden of MR-CBCT soft-tissue matching is minimal.

Soft-tissue matching facilitates the assessment of the prostate target and seminal vesicle coverage and organ at risk position by the therapeutic radiographer, which is particularly relevant with variable bladder and rectal filling.[17] It also avoids an invasive procedure for the patient with a significant infection risk.[5] 66 % of UK centres already use soft-tissue matching for online IGRT in a conventional MR-CT prostate radiotherapy pathway.[6]

Conclusion

In conclusion, there was no clinically significant difference between soft-tissue matching and fiducial matching in MR-only prostate radiotherapy in either overall position or inter-observer variability. Soft-tissue image matching removes the need of an invasive procedure for patients and enables extending MR-only radiotherapy pathways to other pelvic tumour sites where fiducial markers cannot be used. This study provides greater confidence that patients treated in an MR-only pathway receive accurate IGRT with soft-tissue matching and radiotherapy centres who currently use fiducial markers may wish to consider changing practice.

Conflict of interest

None.

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