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Patient position verification in magnetic-resonance imaging only radiotherapy of anal and rectal cancers

David Bird [a,b,*,1], Matthew Beasley [a,3], Michael G. Nix [a,2], Marcus Tyyger [a,4], Hazel McCallum [d,e], Mark Teo [a], Alexandra Gilbert [a,b], Nathalie Casanova [a], Rachel Cooper [a], David L. Buckley [c], David Sebag-Montefiore [a,b], Richard Speight [a,3], Ann M. Henry [a,b], Bashar Al-Qaisieh [a]

[a] Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[b] Radiotherapy Research Group, Leeds Institute of Medical Research, UK
[c] Biomedical Imaging, University of Leeds, Leeds, UK
[d] Northern Centre for Cancer Care, Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK
[e] Centre for Cancer, Newcastle University, UK

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ABSTRACT

Background and Purpose: Magnetic resonance (MR)-only treatment pathways require either the MR-simulation or synthetic-computed tomography (sCT) as an alternative reference image for cone beam computed tomography (CBCT) patient position verification. This study assessed whether using T2 MR or sCT as CBCT reference images introduces systematic registration errors as compared to CT for anal and rectal cancers.

Materials and Methods: A total of 32 patients (18 rectum,14 anus) received pre-treatment CT- and T2 MR-simulation. Routine treatment CBCTs were acquired. sCTs were generated using a validated research model. The local clinical registration protocol, using a grey-scale registration algorithm, was performed for 216 CBCTs using CT, MR and sCT as the reference image. Linear mixed effects modelling identified systematic differences between modalities.

Results: Systematic translation and rotation differences to CT for MR were −0.3 to + 0.3 mm and −0.1 to 0.4° for anal cancers and −0.4 to 0.0 mm and 0.0 to 0.1° for rectal cancers, and for sCT were −0.4 to + 0.8 mm, −0.1 to 0.2° for anal cancers and −0.6 to + 0.2 mm, −0.1 to + 0.1° for rectal cancers.

Conclusions: T2 MR or sCT can successfully be used as reference images for anal and rectal cancer CBCT position verification with systematic differences to CT $<\pm 1$ mm and $<\pm 0.5°$. Clinical enabling of alternative modalities as reference images by vendors is required to reduce challenges associated with their use.

1. Introduction

The potential benefits of magnetic resonance (MR)-only radiotherapy treatment planning have been well documented, as has the need to generate synthetic computed tomography (sCT) datasets to allow treatment dose to be calculated [1–3]. Standard radiotherapy pathways also include cone beam computed tomography (CBCT) patient position verification using computed tomography (CT)-simulation as the reference image. Therefore MR-only treatment pathways must use either the MR-simulation or sCT instead. However, there is limited assessment within the current literature of CBCT registration accuracy [4] when using sCT or MR as the reference image, with the majority of those assessing prostate [5–10] CBCT patients, with Kemppainen [6] also assessing gynaecological patients. These assessments can be used as a bench mark level of acceptability for other pelvic sites with mean 3D translational differences between MR/sCT and CT of $<\pm 2$ mm.

* Corresponding author at: Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK.
E-mail address: David.Bird3@nhs.net (D. Bird).

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However, rectum and anus cancer sites have increased complexity as compared to prostate treatments including; male and female anatomy, greater tumour position variation and larger treatment volumes [11]. Additionally prostate CBCT registrations can be undertaken using fiducial markers, removing the need for soft tissue registration [12]. The independent assessment of CBCT registrations for anal and rectal cancer sites is required prior to MR-only clinical implementation.

To the authors knowledge no studies have assessed CBCT patient positioning accuracy in a MR-only workflow for anal cancers, while two studies have assessed rectal cancer CBCT patient positioning using sCT, but not MR, as a reference image [13,14]. Maspero et al and Tyyger et al assessed the use of sCTs generated by commercially available sCT models using clinically available CBCT positioning software for ten (seven male, three female) and seven (all male) rectal cancer patients respectively. Their findings suggested that sCT could be utilised as a reference image for rectal CBCT registrations, with Maspero's [13] mean differences in translations and rotations when using sCT vs. CT $<\pm 1$ mm and $<\pm 0.5$ ° respectively. However, Tyyger [14] also found in three patients' gross misregistration occurred when using the sCT and both studies had limited patient numbers, including only 3 female patients.

Previously, we described the validation of a deep-learning based sCT model on a cohort of anal and rectal cancer patients using a T2 MR sequence [11] with mean dosimetric difference to CT of 0.1% (range −0.5% to + 0.7%) [11].

Here we aimed to assess whether using sCT or T2 MR scans as the reference image for CBCT patient position verification introduced systematic registration errors vs. CT.

2. Methods

2.1. Data collection

This study is part of a wider MR-only radiotherapy study: "Mri-only treAtmeNT planning for Anal and Rectal cAncer radiotherapy" (MANTA-RAY), research ethics committee reference: 18/LO/1298, ISRCTN Registry: ISRCTN82734641. This study included 32 ano-rectal patients (eighteen rectum and fourteen anus; sixteen male and sixteen female; who underwent radical VMAT external beam radiotherapy. Dose, fractionation and the number of acquired CBCTs per patient group were as follows: anal cancer treatments; 53.2 Gy in 28 fractions - eight CBCTs (fractions 1–4 and 4 weekly scans), rectal cancer patients; 45 Gy in 25 fractions - seven CBCTs (fractions 1–4 and 3 weekly scans) and 25 Gy in 5 fractions - five CBCTs (daily). Exclusion criteria included patients with contra-indications to MR.

All patients received planning CT, MR and routine CBCTs acquired in the radiotherapy treatment position with matched bladder filling and immobilisation protocols. Acquisition parameters are shown in Table 1. For the MR scan, coil bridges were used to keep the coils from deforming the patient skin position. Eight CBCTs were deleted from the clinical systems prior to collection for this study so could not be used in the analysis (one rectum CBCT and seven anus CBCTs from four patients).

Mean time between planning CT and MR data acquisition was 15.1 days (range: 0–43 days) as MR scans were for research purposes and scheduled for when the patient had a clinical appointment prior to or during their first two weeks of treatment. The T2-SPACE sequence was acquired in two linked acquisitions, with positional matching and an overlap of 2 cm before being "stitched" together offline into a single sequence with no overlap. This ensured sufficient superior-inferior scan length to cover all the anatomy required for radiotherapy treatment planning, including target volumes and organs at risk (OARs).

2.2. Synthetic-CT generation

MR scans were rigidly registered to their paired CT datasets using the mutual information registration algorithm in Raystation 8b (RaySearch Laboratories, Stockholm, Sweden) and manually assessed to ensure accuracy. The rigidly registered MR was resampled to the CT frame of reference using Raystation 8b's standard tri-linear resampling. An sCT scan was generated from each patient's T2-SPACE MR scan using the deep learning based cGAN sCT model previously described [11]. Fig. 1 shows an example of an axial slice of the CT, MR, sCT and CBCT of a single anal cancer patient used for registration.

Table 1
The scan parameters for patient CT, MR and CBCT scans.

MR	Make & Model	Siemens Aera 1.5 T
	Sequence	3D T2 SPACE
	Resolution	$0.9 \times 0.9 \times 1.5$ mm^3
	Refocusing Flip Angle (°)	160
	TR (ms)	1600
	TE (ms)	211
	Bandwidth (Hz/px)	545
	Echo train length	134
	Longitudinal scan length	Standard: 2 cm inferior of genitalia to L5 vertebra Extended (if high nodal involvement): 2 cm inferior of genitalia to L5 vertebra (~25–35 cm)
	Field of View (Axial)	450×450 mm^2
CT	Make & Model	Philips Brilliance Big Bore
	Resolution	$1.2 \times 1.2 \times 2$ mm^3
	kVp (kV)	120
	X-ray Tube Current (mAs)	135
	Field of View (Axial)	450×450 mm^2
CBCT	Make & Model	Elekta XVI
	Resolution	$1 \times 1 \times 1$ mm^3
	kVp (kV)	120
	X-ray Tube Current (mAs)	32
	Field of View (Axial)	400 mm diameter

2.3. Reference data preparation

The CBCT registration software does not natively accept MR or sCT datasets as a reference image for CBCT registration and the sCT DICOM tags had to be generated to match the CT. The MR and sCT pixel data for each slice was transposed into the matching CT slice pixel DICOM file, with CT DICOM tags and in the CT frame of reference. This allowed the software to recognise the MR and sCT datasets as valid (CT) reference data. This also allowed their use in conjunction with each patient's original treatment structure set and treatment plan. For MR datasets, the "rescale intercept" DICOM header value was adjusted from −1024 to 0 to prevent the MR voxel intensity information being rescaled inappropriately during import.

This process ensured the three datasets; CT, sCT and MR, all in the same frame of reference were ready for import. The reference data scans were imported and all patient routine CBCTs were associated with each reference image scan independently. Correction reference points (the co-ordinates which translations and rotations are centred around) were set to the plan isocentre for each reference scan as per the departmental clinical protocol.

2.4. CBCT matching process

Each patient CBCT scan was registered to each reference scan (CT, MR and sCT) using the clinical matching protocol used in this centre as detailed below. The automated grey value registration algorithm [15] for translations and rotations was applied locally using a clinically relevant clip box, defined on the reference image using anatomical boundaries and PTV position. Clip box protocol parameters varied for anal and rectal cancers respectively according to the local clinical protocols and can be seen in Table 2. Fig. 2 shows examples of rectal and

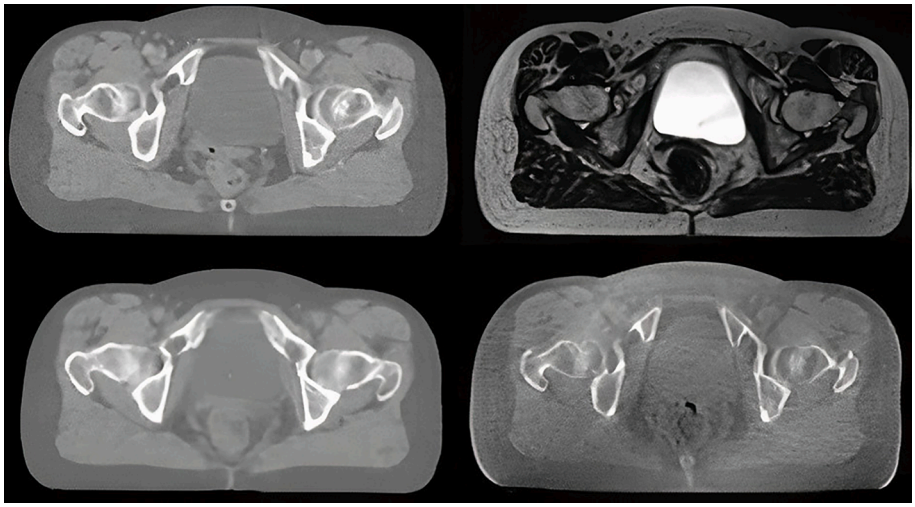

Fig. 1. Example of an axial slice of a single anal cancer patient CT (top left), MR (top right), sCT (bottom left) and CBCT (bottom right) scan used for CBCT registrations.

Table 2
CBCT registration standard protocol clip box size parameters for anal and rectal cancer sites, and the large extended clip box.

Protocol	Dimension	Anatomy to Include	Anatomy to exclude
Anus	Left/Right	Pelvic cavity	Femoral Heads
	Ant/Post	Pubic symphysis	Sacrum
	Sup/Inf	PTV	Sacrum
Rectum	Left/Right	Pelvic cavity	Femoral Heads
	Ant/Post	Sacrum	Pubic symphysis
	Sup/Inf	Whole Sacrum & PTV	X
Extended clip box	Left/Right	Femoral Heads	X
	Ant/Post	Pubic symphysis and Sacrum	X
	Sup/Inf	Pubic symphysis and Sacrum	X

anal clip boxes. All registrations were undertaken by an experienced clinical scientist specialising in radiotherapy imaging. All patient CT registrations were undertaken first, followed by MR and then sCT, with a break of 2 days between any individual patient's CT, MR and sCT registrations being undertaken to reduce operator bias. As approximately 208 registrations were therefore carried out between each individual patient's CT, MR and sCT registrations, this was considered to be a sufficient gap to ensure no registration bias occurred through recollection of a patient's previous registrations.

After each automated registration was carried out, the operator undertook a visual assessment of the registration. In the event of gross errors, an extended clip box was used as described in Table 2 to provide the registration algorithm with additional information to use in the registration process. A simple assessment of intra-observer variability, the variability in one operator carrying out the clip box positioning and any resultant difference in automatic registration, was carried out by repeating the CT, sCT and MR to CBCT registrations for all CBCTs for one anus and one rectum patient (chosen at random) and calculating the variations in each translational and rotational plane between registration one and two.

2.5. Statistical analysis

Linear mixed effects (LME) models in STATA (StataCorp, 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) were applied to the CBCT registration results to assess the effect of reference image (MR or sCT) on the CBCT registrations. MR and sCT were compared to CT which was assumed to be the gold standard as the current clinically used reference image. The LME models calculated the systematic difference in translations and rotations in terms of "effect size" - the systematic shift in each individual translational or rotational dimension from CT when the alternative reference image (MR or sCT) was used. Separate models were applied to anal and rectal cancers as well as for translations and rotations within each cancer site cohort. The LME models used translational distance or rotational angle as the dependent variable; reference image (CT, MR and sCT), dimension (x (left–right/rotation), y (anterior-posterior/pitch) and z(superior-inferior/yaw) and time point (fraction 1–4 or weekly) as fixed effect independent variables and patient as a random effect independent variable. The analysis assessed each translational or rotational dimension separately by applying a contrast interaction between reference image and dimension variables within the model. The models also calculated 95% confidence intervals to provide an assessment of potential error in the systematic differences.

3. Results

The standard clip box protocol produced no gross registration errors for rectal cancer patients or anal cancer patients with sCT or CT reference images. However for 4 anal cancer patients (28% of anal cancer patients) where MR was used as the reference image, gross registration errors were detected. For these patients, 16/32 CBCT registrations (15% of the total anal cancer MR registrations) were affected. The use of the extended clip box protocol in these cases produced successful registrations with no gross errors.

For translations the systematic effect of using sCT and MR vs. CT were between −0.6 and 0.8 mm and −0.4 and 0.3 mm respectively. For rotations, the systematic effect of using either sCT or MR vs. CT was between −0.1 and 0.2° and −0.1 and 0.4° respectively. Maximum 95% confidence intervals were −1.2 and 1.5 mm and −0.5 and 0.7° for translations and rotations respectively. Table 3 shows the results of the LME modelling and Fig. 3 shows each individual CBCT registration difference of MR/sCT from CT and includes outlier differences in registration of 4–6 mm.

Mean intra-observer variability for all CBCTs from a single anal cancer patient was found to be −0.1 mm and 0.1°, 0.1 mm and 0.0°, and 0.3 mm and 0.1° for CT, sCT and MR respectively. Mean intra-observer variability for all CBCTs from a single rectum patient was found to be 0.0 mm and 0.0° for CT, sCT and MR respectively.

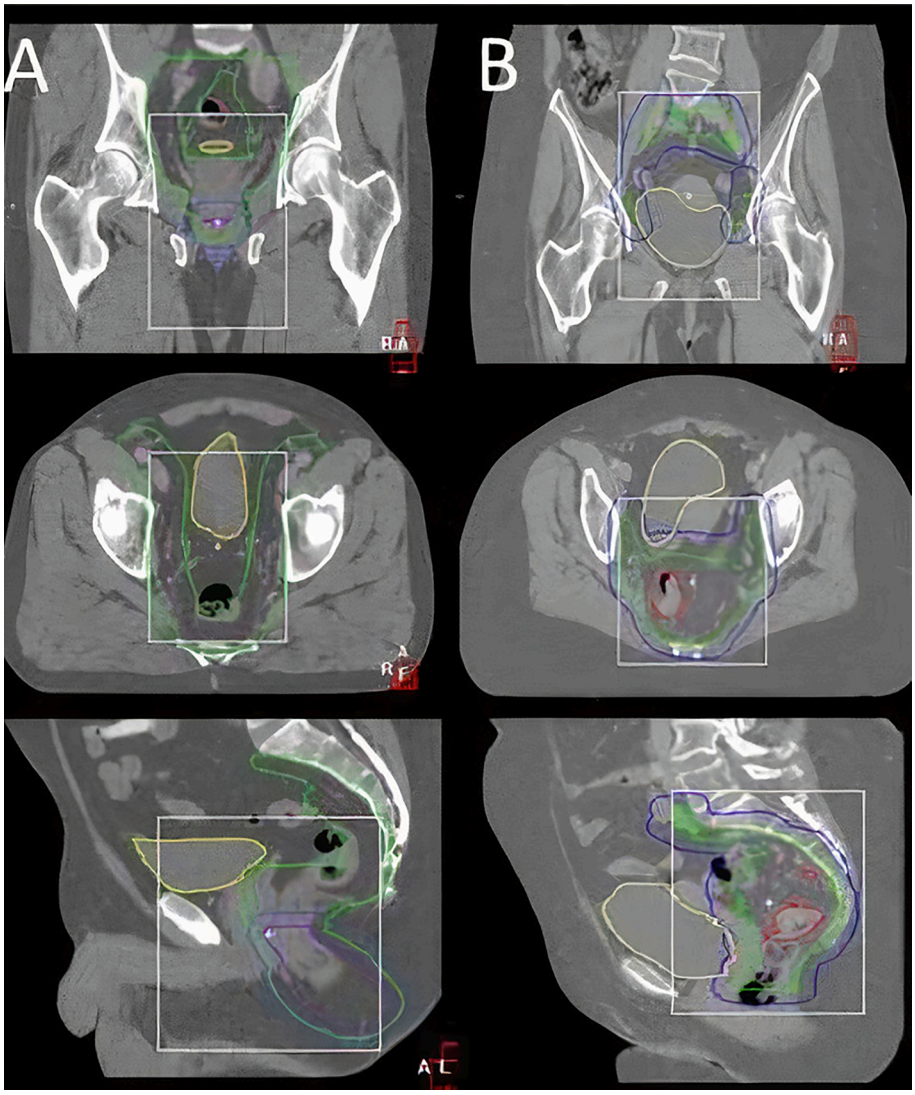

Fig. 2. Example CBCT registration clip boxes for anal (A) and rectal (B) cancer sites respectively as positioned on a reference CT image.

Table 3
The translational and rotational (x (left–right/rotation), y (anterior-posterior/pitch) and z(superior-inferior/yaw)) effect sizes and 95% confidence intervals from the linear mixed effects modelling for MR and synthetic-CT as compared to CT for anal and rectal cancers respectively.

	Reference image (vs. CT)	Dimension	Translations (mm) Effect size (95% confidence intervals)	Rotations (°) Effect size (95% confidence intervals)
Anus	MR	x	−0.3 (−1.0; 0.4)	0.4 (0.1; 0.7)
		y	0.3 (−0.4; 1.1)	−0.1 (−0.4; 0.2)
		z	0.1 (−0.6; 0.8)	0.1 (−0.2; 0.5)
	sCT	x	−0.4 (−1.1; 0.3)	0.2 (−0.1; 0.5)
		y	0.8 (0.0; 1.5)	−0.1 (−0.5; 0.2)
		z	0.3 (−0.4; 1.0)	0.1 (−0.3; 0.4)
Rectum	MR	x	0.0 (−0.6; 0.7)	0.0 (−0.4; 0.4)
		y	−0.4 (−1.0; 0.2)	0.1 (−0.3; 0.5)
		z	−0.3 (−0.9; 0.3)	0.0 (−0.4; 0.4)
	sCT	x	−0.2 (−0.8; 0.4)	−0.1 (−0.5; 0.3)
		y	−0.6 (−1.2; 0.0)	0.1 (−0.3; 0.4)
		z	0.2 (−0.5; 0.8)	0.0 (−0.4; 0.3)

4. Discussion

Standard anal and rectal radiotherapy pathways include CBCT patient position verification using CT-simulation as the reference image. The implementation of MR-only radiotherapy treatment pathways requires that either the MR-simulation or sCT is used for CBCT positional verification. Our findings suggest that MR or sCT can be used for CBCT patient positional verification within an MR-only radiotherapy treatment planning pathway as within a standard of care CT-simulation pathway for anal and rectal cancers with minimal impact on registration accuracy.

We found that a subset of MR anal cancer registrations failed to produce acceptable registrations with the standard clip box. It was notable that no issues occurred with any rectal cancer patients or sCT registrations. A possible cause is the combination of the smaller range of anatomy included in the anal cancer clip box and the use of MR. These gross errors were easily detected through operator registration checks which are always advised for an automated registration process, but it does suggest that additional care is needed for MR registrations or adjustments to the anus MR clip box clinical protocols are needed.

The argument in favour of using MR rather than sCT as a reference image includes firstly that MR data is the visualisation of “real” tissue, and secondly that a sCT is a representation of CT scan, there will be a loss of image quality and soft tissue detail compared to MR. However,

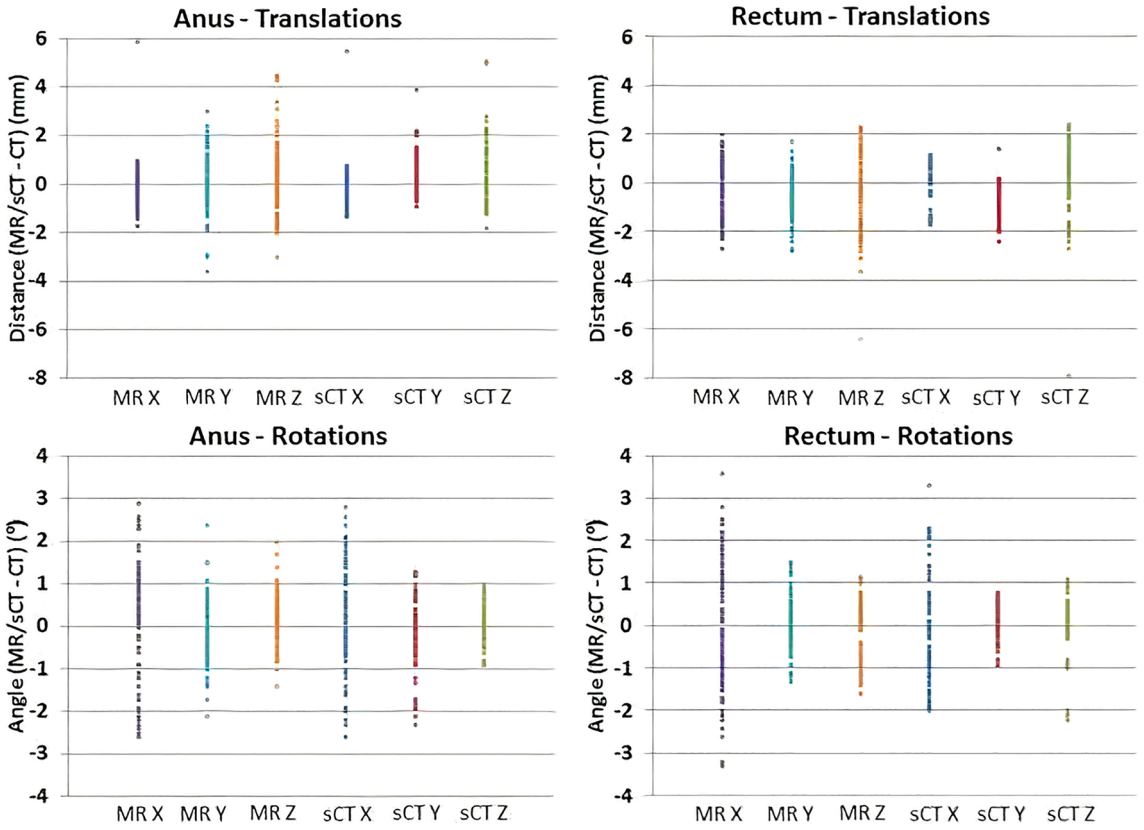

Fig. 3. The translational and rotational (x (left–right/rotation), y (anterior-posterior/pitch) and z(superior-inferior/yaw)) MR and sCT CBCT registration differences to CT for anal and rectal cancer sites, where differences were calculated as the MR or sCT value minus the CT value.

counter-arguments include that using MR with improved soft-tissue contrast that is not present in the CBCT could lead to a false sense of improved accuracy. Furthermore, our findings suggest that using a deep-learning model generated sCT was preferable as the systematic registration errors were no greater than for MR, and in addition resulted in no gross registration errors unlike for the MR datasets. A potential method to combine the benefits of both imaging modalities, would be to register based on the sCT but then inspect the quality of the registration using both the MRI and sCT datasets.

The challenge facing the use of MR or sCT as a reference image is that commercially available CBCT registration software are not CE marked for the use of reference images from different imaging modalities, and do not currently accept MR data without processing such as we did here. Although it is possible to utilise MR without vendor support it has complexities which require centres to accept greater risk attached to its use. Greater investment, support and development from commercial vendors would enable MR-only radiotherapy pathways to maximise their benefit and to continue to progress into clinical use. It is also the responsibility of radiotherapy centres to provide more evidence that further development is required and that utilising MR for positional registration is a safe and geometrically accurate option.

Our results are in line with those in the literature, whether comparing against the baseline findings from prostate studies [5–10] or the more relevant rectum study findings of Maspero [13] and Tyyger [14]. We found the systematic impact of sCT and MR on translations and rotations were $<\pm$ 1 mm and $<\pm 0.5^{\circ}$ similarly to Maspero for sCT reference images. Therefore we can suggest that sCTs, whether generated from deep learning voxel based models such as ours or bulk density models, have similar results for CBCT position registrations. We extend this with our MR findings and a strength of this work is that it includes a larger patient cohort with an equal number of female and male patients such that it more accurately represents the range of anatomy found within a clinical population. It should be noted that the rigid registrations undertaken in the data preparation had the potential to introduce systematic errors into this study, while these were minimised by the assessment of the registrations by an experienced clinical scientist, it is likely some component of the residual systematic errors identified here are due registration error introduced at that point.

It can be seen from Fig. 3 that despite the small systematic differences between reference image modalities, there was a large range of random differences between CT and MR/sCT and that there are some poor registration outliers. This is unlike Maspero, who found no sCT registrations had differences of $>\pm 2$ mm and $>\pm 1.2^{\circ}$. One explanation is that the registration algorithm varied between our studies, where Maspero used a bony chamfer matching algorithm vs. the grey value algorithm used here which explains Maspero's lack of outlier registrations as bony matches are more reproducible. However, the range of registration errors seen in this study has most likely been caused by changes in patient position between CT and MR, which can occur over short time frames, but also would be exacerbated by our mean time between CT and MR scans of 15 days. This is also markedly different to Maspero, where all CT and MR datasets were acquired within 3 h of each other which will have had an impact in limiting intra-patient anatomical changes between scans. This is a limitation of the study as it would have been preferable to limit CT & MR scanning to the same day; however this was not achievable in our data collection due to MR scanner availability.

This limitation increases the importance of using linear mixed effect modelling for analysing our data, as it can take into account the large random fluctuations to find the underlying systematic differences between reference images. An alternative option for mitigating the impact of the variation in patient position between the CT and MR/sCT data would have been to register the MR to the CT using a deformable registration, rather than a rigid registration. However this would have augmented the MR (and therefore also sCT) anatomy, potentially

masking the systematic differences in registrations between MR/sCT and CT.

We carried out a simple assessment of intra-observer variability by repeating the CT, sCT and MR to CBCT registrations for all CBCTs for one anus and one rectum patient and found that the intra-observer variability was negligible for each reference image (CT, sCT and MR). This gives us confidence that further intra-observer variability measurement would not change our findings. Here we did not assess manual registrations which were beyond the scope of this study, however it is reasonable to consider manual registrations to be more subjective than automatic registrations and further assessment would be beneficial.

This study found that using sCT or T2-SPACE MR sequences as reference images for CBCT registration resulted in minimal systematic differences compared to CT ($<\pm1$ mm and $<\pm0.5^{\circ}$), suggesting that from a treatment setup point of view that MR-only radiotherapy can be considered as equivalent to CT-based radiotherapy. A remaining barrier to wide-spread clinical implementation is the clinical enabling of alternative modalities as reference images by vendors to reduce the challenges associated with their use.

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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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