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Original Article

Multicentre, deep learning, synthetic-CT generation for ano-rectal MR-only radiotherapy treatment planning

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ABSTRACT

Background and purpose: Comprehensive dosimetric analysis is required prior to the clinical implementation of pelvic MR-only sites, other than prostate, due to the limited number of site specific synthetic-CT (sCT) dosimetric assessments in the literature. This study aims to provide a comprehensive assessment of a deep learning-based, conditional generative adversarial network (cGAN) model for a large ano-rectal cancer cohort. The following challenges were investigated; T2-SPACE MR sequences, patient data from multiple centres and the impact of sex and cancer site on sCT quality.

Method: RT treatment position CT and T2-SPACE MR scans, from two centres, were collected for 90 ano-rectal patients. A cGAN model trained using a focal loss function, was trained and tested on 46 and 44 CT-MR ano-rectal datasets, paired using deformable registration, respectively. VMAT plans were created on CT and recalculated on sCT. Dose differences and gamma indices assessed sCT dosimetric accuracy. A linear mixed effect (LME) model assessed the impact of centre, sex and cancer site.

Results: A mean PTV D95% dose difference of 0.1% (range: −0.5% to 0.7%) was found between CT and sCT. All gamma index (1%/1 mm threshold) measurements were >99.0%. The LME model found the impact of modality, cancer site, sex and centre was clinically insignificant (effect ranges: −0.4% and 0.3%). The mean dose difference for all OAR constraints was 0.1%.

Conclusion: Focal loss cGAN models using T2-SPACE MR sequences from multiple centres can produce generalisable, dosimetrically accurate sCTs for ano-rectal cancers.

The potential benefits of magnetic resonance (MR)-only radiotherapy treatment planning have been well documented, as has the need to generate synthetic-CT (sCT) datasets to allow treatment dose to be calculated [1,2]. Commercial sCT solutions are available however a recent systematic review found that comprehensive dosimetric analysis is required prior to the clinical implementation of pelvic MR-only sites, other than prostate, due to the limited number of site specific synthetic-CT dosimetric assessments in the literature [3].

For pelvic MR-only sites, rectum and anus cancer sites have increased complexity compared to prostate treatments as they include male and female anatomy, greater tumour position variation and larger treatment volumes. To our knowledge, no studies have assessed sCT dosimetric accuracy for anus treatments, while a small number of studies have assessed rectum sCTs using a mix of research and commercially available sCT solutions [4–9]. All dosimetric results were found to be clinically acceptable, however these studies only assessed small, <12, [6–9], or medium, 15–20 [4,5], patient numbers and small numbers of female patients (range 0–9).

The majority of pelvic sCT methods, including commercial products such as the Philips (Philips Healthcare, Ohio, USA) MRCAT [10], use a T1 DIXON MR sequence as it provides good fat-muscle-bone contrast and all previously reported rectum sCT studies used this sequence. However because T2 sequences are optimal for ano-rectal GTV delineation [11–13], for a T1 DIXON sCT generation solution to be used clinically, a T2 sequence must also be acquired. Requiring a second sequence reduces scanning efficiency and can reduce the treatment accuracy by introducing inter-scan

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Table 1
The MR and CT scan parameters for Centre A and centre B.

		Centre A	Centre B
MR	Make & Model	Siemens Espree 1.5 T	Siemens Aera 1.5 T
	Sequence	3D	3D
	Resolution	1.4 × 1.4 × 1.5 mm	0.9 × 0.9 × 1.5 mm
	Refocusing Flip Angle (°)	160	160
	TR (ms)	1500	1600
	TE (ms)	211	211
	Bandwidth (Hz/px)	600	545
	Echo train length	105	134
	Field of View (Superior-Inferior)	216 mm	Inferior: 2 cm inferior of genitalia Superior: superior aspect of L5 vertebra or greater as required
	Field of View (Axial)	450 × 450 mm^2	450 × 450 mm^2
CT	Make & Model	Siemens Sensation Open	Philips Brilliance Big Bore
	Resolution	1.1 × 1.1 × 3 mm	1.2 × 1.2 × 2 mm
	kVp (kV)	120	120
	X-ray Tube Current (mAs)	122	135

changes including; motion, anatomical changes and registration errors to the pathway. Ideally a single T2 sequence would be used for pelvic sCT generation and target volume and organ delineation, such as the T2-SPACE (Sampling Perfection with Application optimised Contrasts using different flip angle Evolution) sequence which is used within the Spectronic Medical AB (Helsingborg, Sweden) commercial prostate solution [14]. Additionally, only one of these rectal sCT studies, Maspero [6], applies a deep learning approach to sCT generation which are hypothesised to providing more image contrast and detail within the sCT [15–17].

Here, we comprehensively assess a conditional generative adversarial network (cGAN) sCT model, with a focal loss function designed to enhance performance in the hard to predict bone region. Absolute and dosimetric performance of this cGAN sCT model is quantified for a large ano-rectal cohort, to give confidence that ano-rectal sCT generation can be successful and is viable for clinical use, where clinical acceptability is considered to be a dosimetric difference of ±2% [18]. This work addresses a number of challenges to sCT generation including; the use of a routine T2-SPACE MR sequence for sCT generation, the utilisation of patient data from multiple centres and the impact of male vs. female anatomy and of cancer site, anal vs. rectal, on the sCT output, whilst simultaneously addressing the persistent issue of poor cortical bone density estimation.

Method

Data acquisition

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 (REC) reference: 18/LO/1298, ISRCTN Registry: ISRCTN82734641, funded by the National Institute for Health Research (NIHR): ICA-CDRF-2017-03-005). Paired CT and MR datasets were collected from 90 ano-rectal patients (73 rectum, 17 anus and 54 male, 36 female) from two centres (37 from centre A, 53 from centre B) who were due to undergo radical VMAT external beam radiotherapy and had no contraindications to MRI. Exclusion criteria included patients with artificial hips, and contra-indications to MRI, and as a consequence 2 additional patients who had received MRIs were excluded from this study. Both scans were acquired in the radiotherapy treatment position with matched bladder filling and immobilisation. T2-SPACE MR scan acquisition time varied with scan length with a mean of 5 minutes 20 seconds per acquisition.

Radiotherapy planning CT scans and T2-SPACE MR scans were acquired at both centres with the parameters shown in Table 1. The mean time between CT and MR data acquisition was 7.9 days (range: 0 to 43 days). MR scans were scheduled for a time when the patient had a clinical appointment prior to or during their first two weeks of treatment.

Clinical target volumes and organs at risk (OARs) (rectum; bladder and bowel cavity, anus; small bowel, bladder, femoral heads and genitalia) were delineated on the CT as per our centres standard treatment protocol for each patient's routine treatment prior to being utilised for this study.

sCT model and pre-processing

The paired CT-MR datasets of 46 rectum patients were used to train the sCT model, 22 from centre A, 24 from centre B and 32 male, 14 female. The data was pre-processed by registering the MR to CT with a deformable registration, using patient external and bladder structures as "controlling ROIs", before being resampled to the CT frame of reference in Raystation 8b (RaySearch Laboratories, Stockholm, Sweden). All CT & MR voxels outside the patient external contour were set to an intensity of −1024 and 0 respectively, using the patient external contour generated on each individual dataset. Only image slices with both CT and MR data were used to ensure the data was accurately paired. No gas within the patient external was masked on CT or MR in the training cohort.

The cGAN used a novel focal loss function and was trained for 170 epochs on a Tesla K-80 (Nvidia, California, USA) GPU including the use of augmentation, A fuller description of the cGAN model and rationale for its use can be seen in appendix A.

Test data

CT and MR data for 44 patients; 15 rectum from centre A (7 male, 8 female), 17 anus (9 male, 8 female) and 12 rectum (6 male, 6 female) from centre B, were used as test data. Test MR datasets were registered to the CT and masked using the same process as for the training data. Deformable registration was chosen for the test data as it removed the majority of inter-scan patient position differences between the CT and MR scans. The sCT data (DIR sCT) were generated using the model described above in section 2.2.

The DIR sCTs were imported into Raystation 8b and were inherently registered to the CT. New patient external contours were generated for each sCT, all other target volumes and OARs were copied

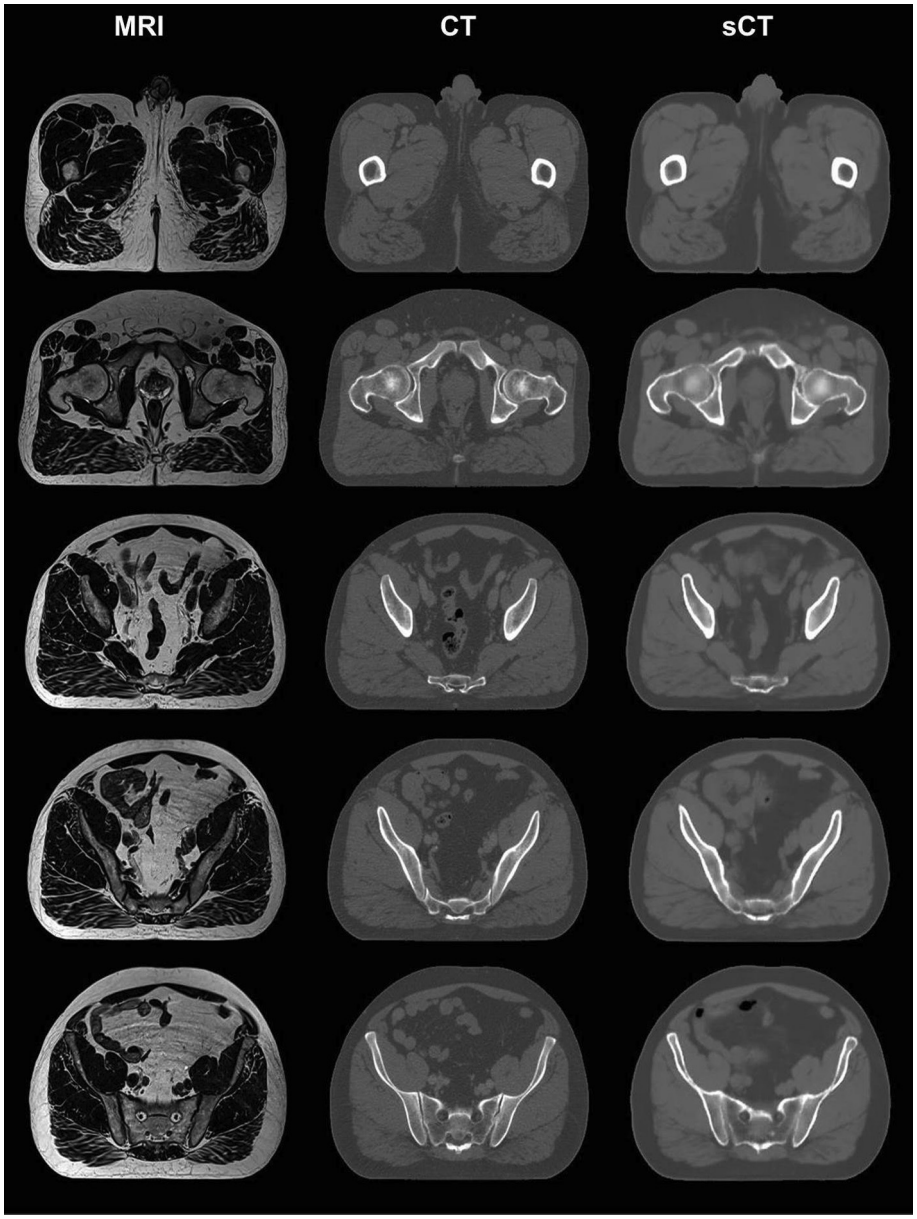

Fig. 1. Matched T2-SPACE MR (left), CT (middle) and sCT (right) slices from an anal cancer patient, where the CT and MR have been deformably registered prior to sCT generation.

from the CT to the sCT, and as such they were identical on each dataset, using the standard tool within Raystation 8b. All bowel gas was masked for CT and sCT datasets at a threshold of −200 HU and set to water density (1 g/cm^3) to ensure consistency with the methodology of previous rectal sCT studies [4–6].

A second testing dataset was generated, where the MR data was registered rigidly, rather than using deformable registration as previously, to the CT data prior to sCT generation (RIR sCT). Masking was carried out using the rigidly registered MR patient external. Analysis was carried out on both data sets.

Assessing sCT quality

HU analysis

Hounsfield Unit (HU) accuracy was determined by computing the mean absolute error (MAE) and mean error (ME) in the (overlap) patient external volume and also in a region thresholded to >150 HU on each CT dataset to represent bony anatomy. Thirteen patients with bowel CT contrast or metal implants of any type were excluded from this specific analysis.

Plan generation & dosimetric analysis

VMAT plans, following departmental clinical protocols, were created and optimised for each patient's CT scan, clinical treatment target volumes and OARs, in Raystation 8b, using the collapsed cone photon algorithm on a dose grid of $3 \times 3 \times 3$ mm^3. Rectum plans were prescribed as either 45 Gy in 25 fractions or 25 Gy in 5 fractions to the PTV chosen according to their clinical treatment and anus plans were a simultaneous integrated boost technique with 53.2 Gy and 40 Gy in 28 fractions prescribed to the primary and elective PTVs respectively. Each CT plan was subsequently recalculated, without reoptimisation, on the sCT.

Dosimetric differences between doses calculated on the CTs and sCTs were assessed through primary PTV dose statistics, D95%,

D50% and D2%, for each plan. Global dose gamma index calculations between the CT and sCT were also performed for 3%/3 mm, 2%/2 mm and 1%/1 mm thresholds. The gamma indices were calculated using a region of interest defined as voxels within a dose threshold of 20% of the target prescription dose. For anus treatments, where an elective nodal PTV (PTVE) was also present and prescribed 40 Gy, the PTVE D95% differences were also assessed as a further measure of accuracy.

OAR dose statistics were assessed for the 29 patients from centre B to establish the dosimetric accuracy of treatment plan calculations away from the primary PTV. Only patients from centre B were assessed as this ensured consistency in the approach, including scan field of view being sufficient for all OARs, and all OAR contours being delineated using the same clinical protocol. Assessed OARs were bladder and bowel cavity for rectum plans and bladder, small bowel, femoral heads and genitalia for anus plans. The clinical protocol OAR constraint statistics were collected for CT and DIR sCT plans, the absolute differences were calculated between CT and sCT and compared as a percentage of the constraint tolerance level.

Statistical analysis

A linear mixed effect (LME) model was utilised to quantify the statistical significance of dosimetric differences and constrain the effect within 95% confidence intervals between modalities, CT and sCT. The model also allowed the quantification of dosimetric differences of secondary variables within the dataset including; treating centre, patient sex and cancer site. The LME model used: dose (normalised by prescription dose) as the dependant variable; modality, sex, treating centre, cancer site and dose statistic (D95%, D50%, D2%) as fixed variables; and patient as a random variable.

Results

Fig. 1. shows matched T2-SPACE MR (left), CT (middle) and sCT (right) slices from an anal cancer patient, where the CT and MR have been deformably registered prior to sCT generation. For DIR sCTs, mean ME of 0.4 (range: −7.8 to 12.4) HU was observed across the analysed cohort, with mean MAE of 35.1 (range: 27.2 to 40.3) HU. Bone showed a mean ME of −95.5 (range: −290 to −0.6) HU. For RIR sCT, mean MAE, ME, Bone MAE and Bone ME were 44.5, 0.8, 250.2 and −142.1 HU respectively.

Dosimetric DIR sCT results are shown in Table 2 and Fig. 2. All dose differences were found to be less than ±0.8% (Fig. 2). All gamma indices at 1%/1 mm were greater than 99.0%. For anus treatments the mean dose difference for PTVE D95% was 0.1% (SD: 0.1%, range: −0.1% to 0.3%). OAR dosimetric differences (Table 4) were found to be small with a mean difference of 0.1%, (S.D: 0.6%) of the constraint tolerances over all organ measures. The Rigid sCT mean dose difference was similar to the DIR sCT mean dose difference (−0.1% vs. 0.1%), however considerably more variability was seen for Rigid sCTs.

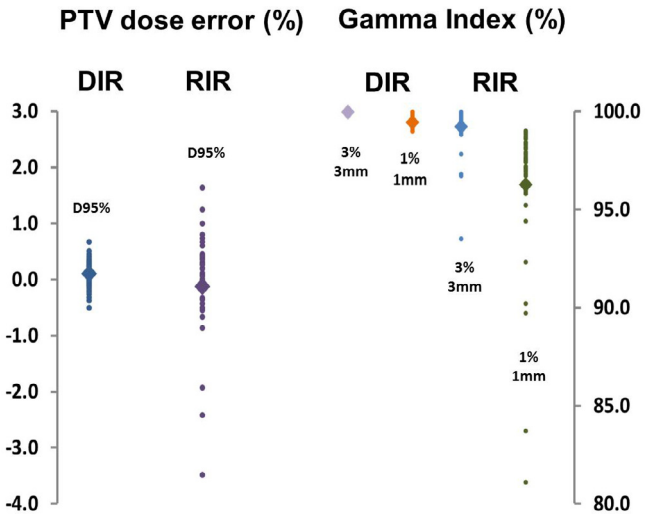

Fig. 2. All (circle) and mean (diamond) PTV dose differences and gamma indices for the DIR and RIR sCTs, where dose differences are calculated as a percentage of the prescription dose.

The LME model found a 95% confidence interval range in dose difference of 0.0% to 0.2% between CT and DIR sCT (Table 3). No significant differences in dose were found between treating centre, cancer site; anal or rectal, or sex, with the maximum effect sizes within 95% confidence intervals showing no clinically significant differences (considered to be <±2%) [18].

Discussion

This study is the first to assess sCT dosimetric accuracy for anal cancer treatments and is the largest known patient cohort for rectal cancer treatments. We found that focal loss driven cGAN-based sCT generation using T2-SPACE MR sequences for ano-rectal cancers achieved excellent sCT quality. Comparing the RIR sCT cGAN results from this study to Maspero et. al. [6], who achieved MAE of 62 HU, our method shows an absolute improvement of ~18 HU. This represents a 40% reduction in HU error across the cohort.

Table 2
DIR test data dose differences and gamma indices for DIR sCTs vs. CTs for all patients and sub-categories; cancer site and sex where dose differences are calculated as a percentage of the prescription dose.

	Number of Patients	Dose constraint	Dose difference (%) mean (S.D) [range]	Gamma Index – mean (S.D) [range]		
				3%/3 mm	2%/2 mm	1%/1 mm
All	44	D95%	0.1 (0.2) [−0.5 to 0.7]	100 (0.1) [99.8 to 100]	99.8 (0.1) [99.3 to 100]	99.5 (0.2) [99.0 to 100]
		D50%	0.1 (0.3) [−0.6 to 0.6]			
		D2%	0.1 (0.3) [−0.6 to 0.7]			
Rectum	27	D95%	0.1 (0.3) [−0.5 to 0.7]	100 (0.0) [99.8 to 100]	99.8 (0.1) [99.5 to 100]	99.5 (0.2) [99.0 to 100]
		D50%	0.1 (0.3) [−0.6 to 0.6]			
		D2%	0.1 (0.3) [−0.6 to 0.6]			
Anus	17	D95%	0.1 (0.2) [−0.2 to 0.5]	99.9 (0.1) [99.8 to 100]	99.7 (0.2) [99.3 to 100]	99.4 (0.2) [99.0 to 99.9]
		D50%	0.2 (0.2) [−0.2 to 0.5]			
		D2%	0.1 (0.2) [−0.2 to 0.5]			
Male	22	D95%	0.1 (0.2) [−0.2 to 0.5]	99.9 (0.1) [99.8 to 100]	99.8 (0.1) [99.5 to 100]	99.5 (0.2) [99.1 to 99.8]
		D50%	0.1 (0.2) [−0.2 to 0.5]			
		D2%	0.1 (0.2) [−0.2 to 0.4]			
Female	22	D95%	0.1 (0.3) [−0.5 to 0.7]	100 (0.0) [99.8 to 100]	99.8 (0.2) [99.3 to 100]	99.4 (0.3) [99.0 to 100]
		D50%	0.1 (0.3) [−0.6 to 0.6]			
		D2	0.1 (0.4) [−0.6 to 0.7]			

Table 3
Linear mixed effects model coefficients and 95% confidence intervals, where dose differences are calculated as a percentage of the prescription dose.

	Dosimetric difference (%)	95% confidence (%)	
		Lower bound	Upper bound
Modality (CT vs. sCT)	0.1	0.0	0.2
Hospital (centre A vs centre B)	−0.1	−0.4	0.1
Site (rectal cancer vs anal cancer)	0	−0.2	0.3
Sex (male vs female)	0	−0.2	0.1

The DIR sCT dosimetric differences to CT (mean +0.1%) and gamma index analysis findings (all patients >99.0% at 1%/1 mm threshold) show an excellent level of agreement. These results suggest the sCT solution is clinically acceptable, while the large testing cohort size which supports confidence that this result is representative of the patient population. The LME model dosimetric difference effect size (0.1%) is also in line with previously published studies (±0.3%) [4–9]. The dosimetric assessment of OAR constraints also found clinically acceptable agreement between sCT and CT (mean difference: 0.1%) suggesting that clinically sufficient sCT dosimetric accuracy extends throughout the entire sCT dataset. These results are also in line with previously reported OAR dose statistics for rectum sCT datasets (mean dose difference: ~0.6%) [5,8].

The assessment of rigidly registered sCTs to CT is a comparison of the "true" MR-only planning sCT, where no image augmentation has occurred, however it also introduces unpredictable inter-scan patient body changes which will impact the dosimetric difference to CT. The mean sCT dose difference of −0.1% vs. CT is more than clinically acceptable, but substantially greater range in the dose difference was seen compared to the DIR sCTs (Fig. 2). This suggests the underlying systematic sCT to CT dose difference is similar to the DIR data, but being masked by the larger random error of these less similar datasets. This larger range of dosimetric difference across the rigid cohort can be explained by the time differences between CT and MR in the test cohort which can cause changes in patient anatomy. This was a limitation of the study that was required to enable successful data collection. A potential issue with using DIR datasets is that the deformable registration may mask an inherent lack of skin tissue visualisation which can occur with MR sequences by matching the CT and MR skin surfaces so any dosimetric differences caused by the inherent skin visualisation will not be represented in the DIR data. However, these differences would be represented in the RIR dataset results and we found the maximum systematic dosimetric impact between CT and MR was −0.1%.

This study suggests that there is no detriment to the sCT image quality or dosimetric accuracy by using T2-SPACE sequences when used in combination with a focal loss GAN-based deep learning model. This is of benefit to improving the efficiency and accuracy of pelvic MR-only planning as it allows a single scan to be used for sCT generation and target volume and OAR delineation. Only using one sequence reduces MR scanning time, making the scan more tolerable for patients and reducing costs and eliminates systematic registration errors between multiple required MRI scans caused by patient position changes. Therefore it would be beneficial if more commercially available pelvic solutions utilised T2 sequences rather than T1 sequences for pelvic sCT generation.

The LME model allowed the assessment of the impact of using data from multiple centres by assessing the 95% confidence interval values of the effect of the associated variables. The small range of effect (-0.4 to +0.1%) between sCTs from centres A and B suggests our cGAN method is capable of producing a generalisable solution for use at multiple centres, in the case that some data from each centre is used in training data. Analogous to this is the situation where a single centre has data from multiple sources – for example multiple MR scanners all with slightly different sequence parameters. This is a beneficial feature as it could allow centres to pool data for sCT model generation making the generation of sCT models more feasible for smaller centres where the required data is harder to collect. We expected differences between sCTs from different centres due to differences in the input MR scans where there was a 3-fold scaling factor and therefore quantisation differences in the low intensity areas of the images (air, bone and muscle) between MRs from centre A and centre B (a further description of the quantisation difference can be seen in appendix A). However, our results are evidence that this model can handle bimodal input data and produce consistent results.

GAN methods such as ours and Maspero [6] do not appear to provide a significant dosimetric improvement compared to other methods [4,5], however in this case it has allowed a more diverse, less-optimal dataset to be utilised to produce a robust, generalisable solution. The HU values of bone are significantly better represented with a focal loss cGAN. This improved bone representation may improve the use of sCTs for CBCT patient treatment positioning and it would be beneficial to investigate this further. A limitation of this study is the use of only one MRI vendor, although different scanner models, at both centres which limits the intensity variability between the matched sequences. It would be of benefit to assess this sCT generation model on a wider variety of input data, including more centres and scanner vendors as this would allow a greater assessment of the model's generalisability.

There are some limitations to generating sCT datasets using a cGAN as in this study, and these relate to training cohort requirements. Training cohorts need to be sufficiently large to produce generalisable and robust results and have accurate registration between CT and MR. This can mean a large cohort of patient data needs to be prospectively acquired which takes time. An additional limitation of cGANs is that once the model is trained, input data for generating sCTs is fixed such that parameters need to remain the same as for the training data. This requires users to be confident regarding their future cGAN model use and MR-only pathways prior to use.

This study shows that T2-SPACE MR sequences from multiple centres can produce generalisable, dosimetrically accurate, sCTs

Table 4
OAR relative dose differences between DIR sCT and CT plans for each organ constraint for each cancer site. Mean, S.D. and range are calculated as the difference between CT and sCT as a percentage of the constraint tolerance.

	OAR	Dose constraint	Tolerance	Dose difference (%) mean (S.D) [Range]
Rectum	Bowel Cavity	V30/V18	250 cc	0.1 (0.4) [−0.5 to 1.0]
	Bladder	V35Gy/V21Gy	45%	0.0 (0.4) [−0.9 to 0.6]
Anus	Bladder	D35%	45 Gy	0.1 (0.1) [−0.1 to 0.2]
	Small Bowel	D150 cc	50 Gy	0.3 (0.4) [−0.5 to 0.9]
	Femoral Heads	D35%	40 Gy	0.0 (0.1) [−0.1 to 0.3]
	Genitalia	D50%	35 Gy	0.0 (0.2) [−0.6 to 0.4]

with low HU errors, for a large cohort of ano-rectal cancer patients and that a single T2 MR sequence can be used for both target and OAR delineation and sCT generation. Dosimetric differences were minimal and clinically insignificant for both PTVs and OARs. The model, which employed focal loss with a cGAN proved robust to differences in input data such as treating centre, cancer site and patient sex.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.11.027.

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