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Physics Contribution

Comparison of Deep Learning-Based and Patch-Based Methods for Pseudo-CT Generation in MRI-Based Prostate Dose Planning

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Summary

Various methods have recently been developed to generate pseudo-CT images for magnetic resonance imaging–based prostate dose planning. Several generative adversarial networks and U-Net deep learning methods with different loss functions and parameters were investigated in this study. In comparison with the patch-based method, these methods appear particularly promising for clinical use, owing to their low image and dose

Purpose: Deep learning methods (DLMs) have recently been proposed to generate pseudo-CT (pCT) for magnetic resonance imaging (MRI) based dose planning. This study aims to evaluate and compare DLMs (U-Net and generative adversarial network [GAN]) using various loss functions (L2, single-scale perceptual loss [PL], multiscale PL, weighted multiscale PL) and a patch-based method (PBM).

Methods and Materials: Thirty-nine patients received a volumetric modulated arc therapy for prostate cancer (78 Gy). T_2-weighted MRIs were acquired in addition to planning CTs. The pCTs were generated from the MRIs using 7 configurations: 4 GANs (L2, single-scale PL, multiscale PL, weighted multiscale PL), 2 U-Net (L2 and single-scale PL), and the PBM. The imaging endpoints were mean absolute error and mean error, in Hounsfield units, between the reference CT (CT_{ref}) and the pCT. Dose uncertainties were quantified as mean absolute differences between the dose volume histograms (DVHs) calculated from the CT_{ref} and pCT obtained by each method. Three-dimensional gamma indexes were analyzed.

Results: Considering the image uncertainties in the whole pelvis, GAN L2 and U-Net L2 showed the lowest mean absolute error ($\leq$34.4 Hounsfield units). The mean errors were not different than 0 ($P \leq .05$). The PBM provided the highest uncertainties. Very

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uncertainties, as well as fast calculation time.

few DVH points differed when comparing GAN L2 or U-Net L2 DVHs and CT_{ref} DVHs ($P \leq .05$). Their dose uncertainties were $\leq$0.6% for the prostate planning target Volume $V_{95\%}$, $\leq$0.5% for the rectum V_{70Gy}, and $\leq$0.1% for the bladder V_{50Gy}. The PBM, U-Net PL, and GAN PL presented the highest systematic dose uncertainties. The gamma pass rates were >99% for all DLMs. The mean calculation time to generate 1 pCT was 15 s for the DLMs and 62 min for the PBM.

Conclusions: Generating pCT for MRI dose planning with DLMs and PBM provided low-dose uncertainties. In particular, the GAN L2 and U-Net L2 provided the lowest dose uncertainties together with a low computation time.

Introduction

Magnetic resonance imaging (MRI) is clearly superior to computed tomography (CT) for organ delineation and could therefore improve tumor targeting in dose planning.[1] However, MRI does not provide electron density information that is necessary for dose calculation. To overcome this issue, several methods have been developed to generate pseudo-CTs (pCTs) for MRI-based dose planning.[2,3] These methods can be divided into 4 categories: bulk density methods (BDM)[4-8]; probabilistic methods[9]; atlas-based methods (ABM)[10-17]; and more recently, machine learning methods such as patch-based methods (PBM), including random forest modeling[18-22] and deep learning methods (DLMs).[23-29] The BDMs assign homogeneous densities to the volumes of interest (VOIs) that are manually delineated from the patient's MRI. Probabilistic methods use a probability density function to determine the corresponding Hounsfield Unit (HU) of each voxel of the patient's MRI. The ABMs involve complex nonrigid registrations of CT-MRI atlases with the patient's MRI, followed by a CT fusion step to obtain the pCT. The PBMs select the k closest CT patches from a training cohort for a given MRI patch from the patient. The selected CT patches are then fused to generate the corresponding pCT patch. This process is reiterated for each patient's MRI patch to obtain the whole pCT.

DLMs enable the computational models that are composed of multiple processing layers to learn representations of data with multiple levels of abstraction.[30] Deep learning has recently been introduced in radiation therapy for multiple applications, such as image segmentation, image processing and reconstruction, image registration, treatment planning, and radiomics.[31-37] DLMs have been more recently proposed for pCT generation from MRI.[38-43] They are particularly appealing because of their fast computation time. These methods model relations between the HU values of the CTs and the intensities of the MRIs by training neural networks. Once the optimal network parameters are estimated, the model can be finally applied to a test patient MRI to generate its corresponding pCT. One of the first DLMs for pCT generation from MRI was based on the U-Net architecture (U-Net DLM).[23] More recently, DLMs that use a generative adversarial network (GAN DLM) architecture have also been proposed (Fig. 1),[24,25,27,29,44] with the theoretical advantage of GAN compared with U-Net to provide more realistic pCTs by obtaining an adversarial feedback from a discriminator network. Although GAN and U-Net DLMs provide promising preliminary results, they most often use a standard loss function (L2 and L1 norms), which may also produce blurring and loss of details.[29] Perceptual loss could overcome this issue by mimicking human visual perception using similar features (such as multiscale features), but it has never been investigated in this pCT generation application.[45-47] Network hyperparameters such as layer level, the number and weight associated with each level (for perceptual loss), and the discriminator weight compared with the generator weight can also affect the image accuracy. Overall, all these DLM configurations lack a thorough dose evaluation for pCT generation from MRI.

We previously showed that PBM provided lower imaging and dose uncertainties in the pelvis compared with ABM and BDM.[20] PBM was found to be faster than ABM. In another study, the U-Net DLM with L2 loss function has been shown to provide better imaging results than the ABM, similar dosimetric results as the ABM, and fewer uncertainties than BDM.[48] However, even though the PBMs and DLMs can be considered the most suitable methods for MRI-based dose planning, they have never been compared. Finally, U-Net and GAN DLMs have never been dosimetrically compared in the literature.

This study aims to evaluate and compare the U-Net and GAN DLMs using various hyperparameters and loss functions (L2, single-scale PL, multiscale PL, weighted multiscale PL), in addition to PBM, for prostate cancer MRI-only dose planning.

Methods and Materials

Thirty-nine patients received a volumetric modulated arc therapy for localized prostate cancer. The ethics approval for the study protocol was provided by the local area health ethics committee, and informed consent was obtained from

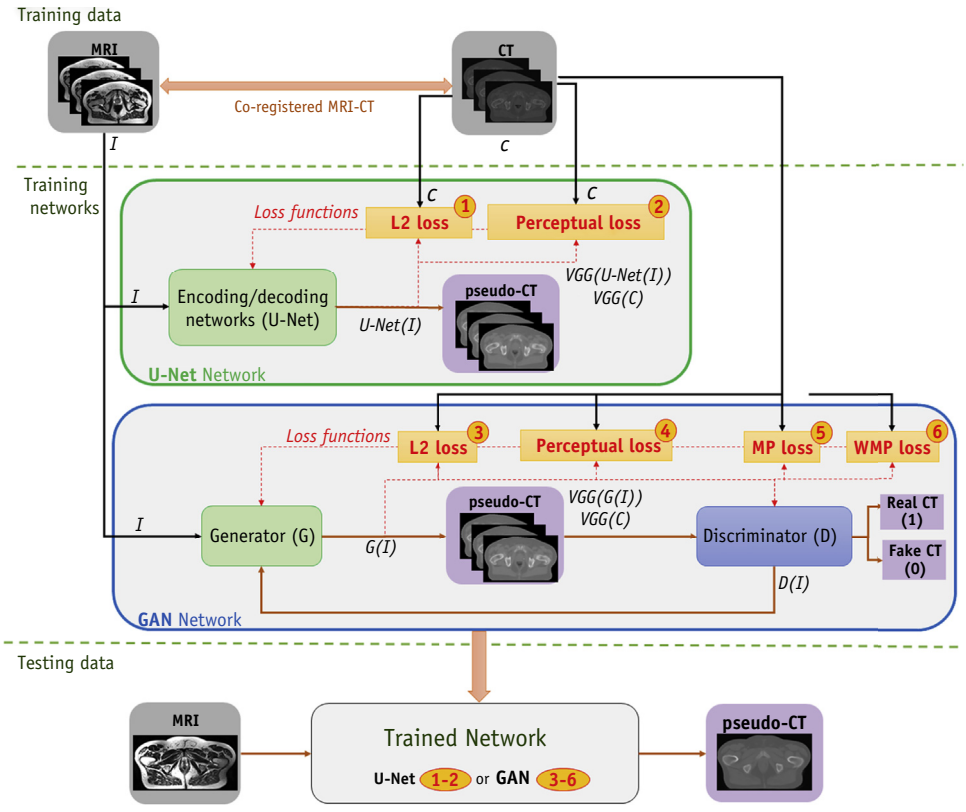

Fig. 1. U-Net and generative adversarial network (GAN) deep learning—trained architectures with different implemented loss functions. *I* corresponds to the training MRI and *C* to the corresponding training CT. Two deep learning neural networks (U-Net and GAN) were trained with 4 loss functions (L2 loss, single-scale perceptual loss, multiscale perceptual [MP] loss, and weighted multiscale perceptual [WMP] loss) yielding 6 different deep learning training strategies: U-Net with L2 loss (U-Net L2), U-Net with single-scale perceptual loss (U-Net PL), GAN with L2 loss (GAN L2), GAN with single-scale perceptual loss (GAN PL), GAN with multiscale perceptual loss (GAN MPL), and GAN with weighted multiscale perceptual loss (GAN WMPL). For each patient from the training database, the CT and MRI training images were first nonrigidly coregistered. The deep learning method (DLM) architecture of the U-Net was symmetrical, with N encoding and decoding units each. The contracting path consisted of 12, 3×3 convolution layers with stride 2 for down-sampling, each followed by batch normalization and ReLU activation function. To train the U-Net DLM, 2 different loss functions were implemented: L2 loss and single-scale perceptual loss. The VGG16 network was used to compute the features inside the CT and pseudo-CT (pCT) images. The training of the GAN consists of 2 competing multilayer networks: the generator and the discriminator. The generator is used as a regression model to provide pCTs from magnetic resonance images (MRIs). The generator employed in this study has the same architecture than the previously described U-Net. The discriminator aims to distinguish the real image (ground truth) from the realistic fake image (pCT) produced by the generator. The GANs are formulated mathematically as a minimax game between these 2 networks, which is solved by alternating gradient optimization. The input data of the generator are MRI and registered CT images that provide pCTs. Then, the discriminator classifies these pCTs as real or fake CTs until the discriminator cannot determine whether the pCT looks like a real CT or not. In the testing step, for a new given test patient, the MRI goes through the trained network to obtain the corresponding pCT.

all patients.[10] The study follows the same workflow described in our previous study.[20]

Image acquisition

Patients had both an initial CT ($CT_{initial}$) and 3T MRI in the treatment position (Appendix 1, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).[20] The CT scans were acquired with a GE LightSpeedRT large-bore scanner or a Toshiba Aquilion. The MRI was acquired with a 3T Siemens Skyra MRI scanner. For MRI acquisition, 3D T_2-weighted SPACE sequences were considered with the following parameters: TE = 102 ms, TR = 1200 ms, flip angle = 35°, field-of-view = $430 \times 430 \times 200$ mm^3, and voxel size = 1.6 mm^3.

MRI preprocessing and intrapatient CT to MRI registration

The T_2-weighted images were preprocessed for normalization and correction of image nonuniformity (Appendix 2, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).[10,12] Even if the delay between the acquisition of $CT_{initial}$ and MRI was kept as short as possible, the patient's

anatomy could still be different between acquisitions. To minimize these pelvic anatomy variations between CT and MRI,[10] each $CT_{initial}$ was registered to its corresponding MRI by using a rigid registration[49] followed by a nonrigid registration.[50] This registered CT was considered as the reference (CT_{ref}).

For all pCT generation methods, the entire cohort (39 patients) was randomly split 3 times with nonrepeated patients between training (n = 25) and validation cohorts. For validation, the model was trained independently on each of the 3 different training cohorts. The patients in the validation cohorts were all different (14 + 14 + 11 patients, respectively). Thus, the number of patients in the training/validation cohorts were 25/14, 25/14, and 25/11.

PBM for pseudo-CT generation

The PBM is detailed in reference 20 and Appendix 3 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). To summarize, this method can be divided into the 4 following steps.

(1) An interpatient rigid and affine group-wise registration was performed to match all preprocessed MR images into the same coordinate system. Then, the obtained transformations were applied to the corresponding CT images to propagate them into the same coordinate system.

(2) A feature extraction step was performed to obtain spatial, textural, and gradient information from the registered MRI, followed by patch partitioning with overlap.[51] The selected features were the multiscale MR intensities, Shannon entropy, and the norm of the gradient.[51] The patch partitioning was conducted on each feature image and the related CT image. The Cartesian coordinates of the centered location of the patches were used as the spatial information.

(3) An approximate nearest neighbor search model[52] was generated to select the training patches closest to the target MRI patches. Several randomized KD-trees were trained on the full training feature patch set. These KD-trees aimed to organize the feature patches in a data structure, thereby performing the nearest neighbor search more efficiently. The feature patches from the target MRI were iteratively given as the input of the randomized KD-trees. Ten feature patches (from the training cohort) closest to the target feature patches were then successively selected. After each iteration, only the CT patches related to the 10 closest feature patches were stored.

(4) A multipoint-wise aggregation scheme was conducted to generate the pCT patches. For each target feature patch centered at a location v, only the closest related CT patches near v were fused by weighted means. The weights were obtained by computing the normalized Euclidian distances between the target feature patch and the closest feature patches. The weighted mean was used to estimate the pCT HU value at location v.

The PBM was implemented in C++ using the Insight ToolKit library.[53] The training computation time was approximately 24 hours (without GPU and cluster architecture).

DLMs for pseudo-CT generation

Figure 1 depicts the overall workflow of the compared DLMs with distinct implemented loss functions. As illustrated, 2 different networks (U-Net and GAN) trained with different loss functions constituted a set of 6 training strategies: (1) U-Net with L2 loss (U-Net L2); (2) U-Net with single-scale perceptual loss (U-Net PL); (3) GAN with L2 loss (GAN L2); (4) GAN with single-scale perceptual loss (GAN PL); (5) GAN with multiscale perceptual loss; and (6) GAN with weighted multiscale perceptual loss.

U-Net DLM

The U-Net DLM was implemented based upon a 2D architecture similar to the one proposed by Han.[23] This architecture was composed of 2 networks called *encoding* and *decoding parts*. The encoding part aimed to extract the multiscale features from the target MRI. This network was composed of 12 convolutional layers, followed by batch normalization and ReLu activation functions.[54] The filter numbers of these layers were 64, 64, 128, 128, 256, 256, 256, 512, 512, 512, 512, and 512, and the filter size was 3 × 3 (stride = 1). To obtain multiscale information, some of the features were down-sampled using convolutional layers with a filter size of 2 × 2 and stride = 2.

The decoding part aimed to gradually reconstruct the pCT using the features computed in the encoding part. This network was a mirror version of the encoding part. For feature up-sampling, transposed 2D convolutional layers were used with a filter size of 2 × 2 and stride = 2. To obtain the pCT, the last layer of the decoding part was a convolution layer with 1 filter (size = 1 × 1).

One of the differences between our U-Net DLM and the one proposed by Han[23] is how feature map down-sampling and up-sampling were performed. We used 2D convolutional filters (with stride = 2 x 2) and 2D transpose convolutional filters, instead of max pooling and up pooling as suggest by Han.[23] The advantage of using these convolutional filters is that their related weights can be optimized during the training process, allowing computation of new features for better data representation. Conversely, the max pooling is a fixed operation where no new feature is computed. Additionally, we added batch normalization after some convolutional layers to improve the convergence of the loss function during the gradient

descent. Finally, the number of convolutional layers linking the encoding and decoding parts was decreased. The aim of this change was to reduce the blur effect in pCTs, which arises when applying too many convolution filters to the low resolution feature maps.

As shown in Figure 1, to train our U-Net DLM, 2 different loss functions were implemented: L2 loss[23,29] and single-scale perceptual loss.[45] The L1 loss function was not considered in this study because it was used as an evaluation metric (see imaging endpoints section). The L2 loss aimed to minimize the differences between the CT and pCT voxels. This loss function was defined as:

$$L_{U-Net}(I,\ C) = \ \| C - U - Net(I)\|_2^2$$

where I is the MRI, C is the corresponding CT, $U- Net(I)$ is the pCT generated by the U-Net, and $\| \ \|_2^2$ is the L2 norm.

The single-scale perceptual loss mimics the human visual system to compare CT and pCT images using similar features as opposed to only the intensities.[24,45] The VGG16 network was pretrained from the ImageNet data set, available in Keras,[55] and used to compute the features inside the CT and pCT images, The choice of VGG16 was justified because this network is often used for perceptual loss computation in the literature and appears relevant for different tasks (image deblurring, super resolution, etc)[45,55] The perceptual loss function was defined as:

$$L_{U-Net}(I,\ C) = \ \| VGG(C) - VGG(U - Net(I))\|_2^2$$

where VGG is the output of the 7th VGG16 convolutional layer. The choice 7th VGG layer is justified in Appendix 4.1 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).

GAN DLM

The GAN DLM architecture was composed of 2 networks: a generator (G) and a discriminator (D), which were trained in competition with each other and illustrated in Figure 1.

Generator network

The generator network aimed to provide pCTs from the patient MRIs. The generator network used a 2D architecture identical to the previously described U-Net DLM. Besides the previously defined L2[56] and single-scale perceptual loss functions, 2 multiscale versions of perceptual losses were implemented, including a weighted multiscale implementation.

The evenly weighted multiscale perceptual loss aimed to first compute the L2 norm between the CT and pCTs feature for some VGG layers. These layers correspond to each scale change in the VGG architecture. Then, the obtained L2 norms integrated in the perceptual loss were averaged considering the multiscale information of each layer (Appendix 4.2, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). This multiscale perceptual loss was described as:

$$L_G(I,\ C) = \frac{1}{card(S)}\sum_{i\ \in\ S} \| \ VGG_i(C) - VGG_i(G(I))\|_2^2$$

Where $S=\{2,\ 5,\ 7,\ 10,\ 13\}$, I is the MRI, C is the corresponding CT, $G(I)$ is the pCT produced by the generator, VGG_i is the i^{th} VGG16 convolutional layer, and $\| \ \|_2^2$ is the L2 norm.

The weighted version of multiscale perceptual loss follows the same principle as the loss described previously. However, the L2 norms obtained from the VGG layers were weighted to give more importance to the layers yielding the lowest mean absolute error (MAE) (Appendix 4.2, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). The weighted multiscale perceptual loss was described as follows:

$$L_G(I,\ C) = \frac{1}{card(S)}\sum_{i\ \in\ S} w_i \| \ VGG_i(C) - VGG_i(G(I))\|_2^2$$

Where $w_i = e^{-\ (MAE_i(C,\ G(I)))}$ with MAE_i is the mean absolute error between CTs and pCTs generated by the GAN using the i^{th} VGG16 convolutional layer for perceptual loss computation. The considered MAEs were computed inside the whole pelvis.

Discriminator network

The discriminator network aimed to classify the generated pCT image as real or fake CT. Thus, the output of this network is a probability value ranging between 0 and 1 depending on whether the generated pCT seems to be fake or real, respectively. The architecture was composed of 6 convolutional layers and 1 fully connected layer. Each convolutional layer was followed by batch normalization and Leaky-ReLu activation functions. The number of filters for these layers were 8, 16, 32, 64, 64, and 64. The filter size was 3 × 3 (stride = 2) for the first 4 layers and 1 × 1 (stride = 1) for the remaining layers. The fully connected layer had 1 filter followed by a sigmoid activation function.

The loss function of the discriminator was a binary cross entropy[29,45,57] defined as: $L_D(G(I),\ \ C) = \ - \sum_{i=\ 1}^{n} C_i \log\ (G(I)_i) + \ (1 - \ C_i) \log\ (1 - \ G(I)_i)$, where $G(I)$ is the pCT computed by the generator from the target MRI I, C is the corresponding CT, and n is the number of voxels inside the C and I images.

The generator and discriminator losses were combined to form the following adversarial loss: $L_{\text{adversarial}}(I,\ C) = \ \lambda_1 L_D(I,\ C) + \ \lambda_2 L_G(I,\ C)$, where I is the MRI, C is the corresponding CT, $L_D(I,\ C)$ is the discriminator loss, $L_G(I,\ C)$ is the generator loss, and λ_1 and λ_2 are the weights for the discriminator and generator losses, respectively. The discriminator was first trained using the discriminator loss, followed by the generator training using the fully adversarial loss. These training steps were performed iteratively and stopped when the discriminator could not accurately

determine whether the pCTs provided by the generator looked like true or false CTs.

Training of the U-Net and GAN methods

The U-Net and GAN DLMs were trained using anatomically paired data: axial 2D slices of the training CT and MR images (3600 slices). Data augmentation was performed to increase the size of the training cohort. It was conducted by randomly applying affine registrations on the slices (translated by -5% to 5% per axis, rotated by -10° to +10°, sheared by -10° to 10°). A minibatch size of 5 slices and 300 epochs was considered. The choice of this minibatch size is detailed in Appendix 4.3 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). The network parameters were optimized using the Adam algorithm.[58] The parameters of this algorithm were $\alpha = 1 \times 10^{-4}$, $\beta_1 = 0.9$, and $\beta_2 = 0.9$. For the GAN, the weights of the discriminator and generator loss functions were $\lambda_1 = 5$ and $\lambda_2 = 1$, respectively. The convergence curves of the GAN with perceptual loss (generator and discriminator) are presented in Appendix 4.4 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).

The U-Net and GAN DLMs were implemented in Python using Keras.[59] The training computation time of each network was approximately 24 hours with a GPU Nvidia GTX 1070 TI 8 GB.

The stochastic effect on the training of each pCT generation method (U-Net, GAN, and PBM) was assessed by repeating 3 pCT generations (training and validation) for each group (25/14, 25/14, and 25/11) and for each method (Appendix 5, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).

Delineation and dose calculation on reference CT and pseudo-CT

Organ delineation was performed on CT_{ref} by a senior oncologist in agreement with the GETUG/RECORAD group recommendation (Appendix 6, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).[60] The contours were rigidly propagated from CT_{ref} to pCT.

A volumetric modulated arc therapy was planned on the CT_{ref} images with the Pinnacle v.9.10 (Philips) treatment planning system for prostate and seminal vesicles. The collapsed cone convolution algorithm was used for dose calculation. A sequential treatment was delivered with a total dose of 50 Gy to the prostate and seminal vesicles, followed by a boost of 28 Gy in the prostate (at 2 Gy per fraction). GETUG dose−volume constraints were applied to the organs-at-risk (Appendix 6, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).[60] The beam parameters used to compute the dose from CT_{ref} were used to calculate the dose from pCT.

Endpoints and statistical analyses

Imaging and dosimetric endpoints were considered for the 39 patients in a cross validation, using the 7 pCT generation configurations: PBM, U-Net with L2 loss (U-Net L2), U-Net with single-scale perceptual loss (U-Net PL), GAN with L2 loss (GAN L2), GAN with single-scale perceptual loss (GAN PL), GAN with multiscale perceptual loss, and GAN with weighted multiscale perceptual loss.

Imaging endpoints

To compare the imaging accuracy of different pCT generation methods, a voxel-wise comparison of the HU between CT_{ref} and pCT was performed. To accomplish this, the MAE and the mean error (ME) were calculated between the CT_{ref} and pCT obtained from the 7 configurations. These endpoints were defined as: $MAE = \frac{1}{n}\sum_{i=1}^{n}\left|HU_{CTref}(i) - HU_{pCT}(i)\right|$ and $ME = \frac{1}{n}\sum_{i=1}^{n} HU_{CTref}(i) - HU_{pCT}(i)$. They were calculated in the entire body, soft tissues (prostate, rectum, and bladder) and pelvic bones (femoral heads). Table E1 lists the mean HU values of the CT_{ref} inside each VOI.

Dosimetric endpoints

The accuracy of the methods was first evaluated by computing the dose uncertainty (MAE) and systematic dose uncertainty (ME). The dose uncertainty was defined by the differences in mean absolute values across dose volume histograms (DVHs) calculated from the dose on the CT_{ref} and the pCTs. The systematic dose uncertainty was computed as the mean DVH differences between the CT_{ref} and pCT. These uncertainties were reported for the RTOG/GETUG reference DVH points[60,61] and the entire DVH of the VOI (prostate planning target volume, bladder, rectum, and femoral heads). The DVH bin size was 5 cGy. The mean dose (D_{mean}) was also considered. A spatial dose evaluation was finally conducted by performing 3D gamma analyses (local, 1%/1 mm, dose thresholds 10% and 30%) using the dose distributions from CT_{ref} and pCTs.

Statistical analysis

Wilcoxon signed-rank tests were performed to compare the endpoints. For the MAE (image and dose), these tests were used to compare the lowest MAE among all the methods to the MAE of each other method and also to compare MAE of the GAN PL method to the MAE of the U-Net PL. For the ME (image and dose), these tests were used to compare the ME of each method to 0 (null distribution). For the DVH comparisons across the pCT generation methods, a nonparametric permutation test was performed[62] to control the presence of false positives in case of multiple statistical tests (5 cGy DVH bin-wise). In

Table 1 Imaging endpoints comparing the reference CT with the pseudo-CTs obtained by each method for the entire pelvis, soft tissue, and bone

			Methods used to generate pseudo-CT						
				U-Net methods		GAN methods			
		Endpoints (HU)	Patch-based method	L2	PL	L2	PL	MPL	WMPL
Entire pelvis		MAE	44.7 ± 11.4*	34.4 ± 7.7	36.8 ± 6.0*†	34.1 ± 7.5	34.9 ± 6.4*	35.6 ± 6.2*	35.1 ± 6.8*
		ME	9.9 ± 18.1*	-1.0 ± 14.2	3.3 ± 13.6	-1.1 ± 13.7	4.1 ± 13.9	1.9 ± 13.3	1.2 ± 14.0
Soft tissue only	Entire soft tissues	MAE	36.4 ± 11.3*	26.7 ± 6.4	29.2 ± 5.2*†	26.5 ± 6.4	27.1 ± 5.3*	27.8 ± 5.0*	27.4 ± 5.6*
		ME	6.0 ± 19.0	-2.6 ± 14.7	0.9 ± 14.0	-2.8 ± 14.3	1.3 ± 14.8	-0.6 ± 14.1	-1.2 ± 14.8
	Prostate (CTV)	MAE	20.6 ± 6.0*	18.1 ± 5.2	22.2 ± 4.9*†	17.7 ± 4.49	23.3 ± 5.9*	21.6 ± 3.7*	22.9 ± 5.8*
		ME	8.2 ± 15.0*	0.8 ± 12.9	14.4 ± 11.5*	0.3 ± 12.0	16.8 ± 11.5*	12.3 ± 11.2*	13.9 ± 13.8*
	Bladder	MAE	21.1 ± 9.0*	18.6 ±7.4	19.3 ± 10.0	18.8 ± 8.9	19.6 ± 9.3	20.2 ± 10.0	19.9 ± 9.3*
		ME	10.7 ± 14.0*	3.4 ± 13.6	5.3 ± 16.6*	3.7 ± 14.6	7.7 ± 15.5*	3.4 ± 16.4	5.7 ± 16.4*
	Rectum	MAE	78.0 ± 60.5*	65.0 ± 65.7	68.6 ± 66.1†	68.3 ± 64.4	72.9 ± 68.6	69.2 ± 65.5	71.3 ± 68.5
		ME	7.0 ± 73.2*	-24.0 ± 72.5	-17.5 ± 74.1	-20.5 ± 73.6	-11.3 ± 78.9	-16.6 ± 76.3	-16.0 ± 77.2
Bone only	Whole pelvic bone	MAE	143.6 ± 27.8*	125.3 ± 22.0*	126.3 ± 22.1*	123.9 ± 20.6	127.9 ± 22.3*	127.1 ± 21.1*	126.7 ± 21.2*
		ME	58.3 ± 45.5*	20.2 ± 42.3*	32.7 ± 41.8*	19.4 ± 41.4*	39.7 ± 40.8*	31.8 ± 41.4*	28.8 ± 41.3*
	Femoral heads	MAE	109.3 ± 27.0*	102.0 ± 24.4*	103.8 ± 22.5*	100.2 ± 20.4	104.7 ± 21.5*	104.9 ± 19.2*	104.6 ± 20.9*
		ME	36.5 ± 49.9*	5.0 ± 49.5	21.9 ± 48.8*	5.1 ± 47.2	29.8 ± 48.0*	16.9 ± 48.1*	19.6 ± 48.0*

Abbreviations: CTV = clinical target volume; MAE = mean absolute error; ME = mean error; GAN = generative adversarial network; U-Net L2 = U-Net using a L2 loss; U-Net PL = U-Net using a single-scale perceptual loss (layer 7); GAN L2 = generative adversarial network using a L2 loss; GAN PL = generative adversarial network using a single-scale perceptual loss (layer 7); GAN MPL = generative adversarial network using a multiscale perceptual loss; GAN WMPL = generative adversarial network using a weighted multiscale perceptual loss.

The imaging endpoint values are expressed as mean ± standard deviation.

* The Wilcoxon test was used, first to compare the MAE of the GAN with L2 loss to those of the other methods, and second to compare the ME of the methods to a null distribution. Significant differences were considered at $P \leq .05$.

† The Wilcoxon test was also used to compare the MAE of the GAN with perceptual loss to those of the U-Net with perceptual loss. Significant differences were considered at $P \leq .05$.

this case, 1000 permutations were performed where for each permutation *i,* randomly selected DVHs were swapped (CT_{ref} to pCT, and vice versa) and the average difference was computed for each dose-bin. For each permuted sample and the original sample, the average difference was then normalized to the standard deviation computed over all the 1000 permutations and the maximum observed difference was selected as test-statistic (TS). A distribution of TS across all the permuted samples ($TS_{i,max}$) was obtained and compared with the one from the observed sample (TS_{max}). The adjusted P value was therefore computed as the probability of having a TS_{max} greater than the $TS_{i,max}$ compared with a significance level of 5% ($P \leq .05$). The corresponding percentile over the distribution of all the $TS_{i,max}$ gives a threshold value that determines the dose DVH bins where statistically significant dose difference arises. Unlike bin-wise tests, the permutation test gives a single number that summarizes the discrepancy of the DVHs between the 2 groups, rather than the discrepancy of a particular bin and, therefore, it accounts for multiple comparisons. The mathematical formulation of the permutation test can be found in Chen et al.[63] The test allowed us to report a robust bin-wise comparison across the DVH value of each method, but also to compare the lowest MAE among all the methods to the MAE of each method and the ME of each method to 0.

The Friedman test was used to compare the MAE or the ME of each pCT method between the 3 different trainings (1, 2, and 3; Appendix 5, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). Results were considered as significant when $P \leq .05$.

Results

Imaging endpoints and calculation time

Examples of MRI, CT_{ref}, and pCTs generated by each method are illustrated in Figure E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).

Table 1 lists the imaging endpoints corresponding to each pCT generation method for the VOIs. The GAN L2 and U-Net L2 showed the lowest MAE and ME (in absolute value) for soft tissue and bone. The GAN PL showed significantly lower MAE for the whole pelvis and the soft tissue than the U-Net PL. The PBM provided the highest corresponding values. Except for the bone, the MEs of GAN L2 and U-Net L2 were not significantly different from a null distribution. Assessing the stochastic effect, the 3 measurements by method confirmed that GAN L2 and U-Net L2 provided the lowest image uncertainties (Appendix 5, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).

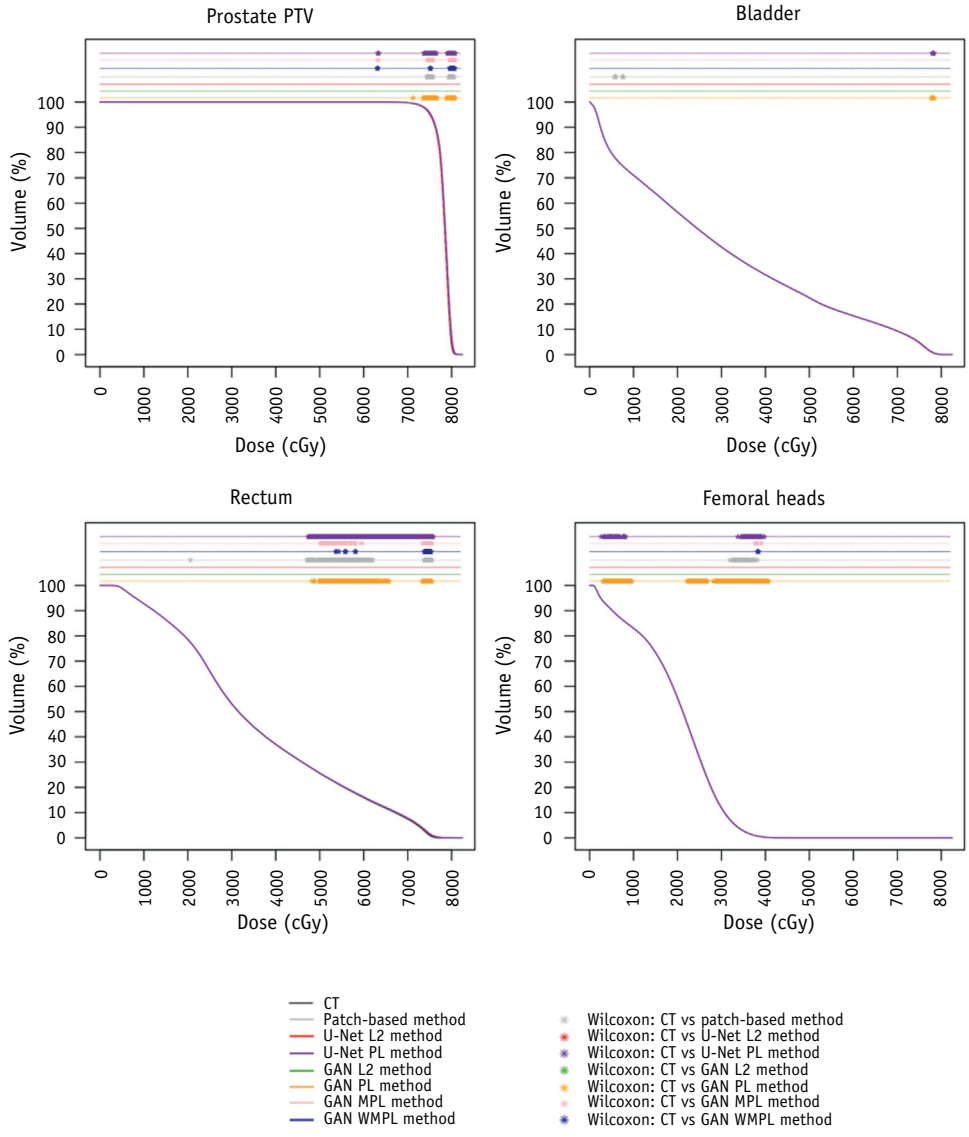

Fig. 2. Mean dose−volume histograms (DVHs) for prostate planning target volume (PTV), bladder, rectum, and femoral heads from the reference computed tomography (CT) and pseudo-CTs generated by each method. Permutation tests were used to compare the DVHs from the reference CT to those of the pseudo-CT generation methods. *Significant differences ($P \leq .05$) between the DVHs. *Abbreviations*: U-Net L2 = U-Net using a L2 loss; U-Net PL = U-Net using a single-scale perceptual loss (layer 7); GAN L2 = generative adversarial network using a L2 loss; GAN PL = generative adversarial network using a single-scale perceptual loss (layer 7); GAN MPL = generative adversarial network using a multiscale perceptual loss; GAN WMPL = generative adversarial network using a weighted multiscale perceptual loss.

The mean calculation time to generate 1 pCT was 15 seconds for the DLMs and 62 minutes for the PBM (without using cluster architecture or GPU parallelization).

Dosimetric endpoints

Figure 2 shows the mean DVHs for the CT_{ref} and each method by VOI. No DVH points significantly differed when comparing GAN L2 or U-Net L2 DVHs and CT_{ref} DVHs. Most of the points with significant differences were observed for the PBM, GAN PL, and U-Net PL.

Figure 3 displays the dose uncertainties (MAE) of each method along the DVHs by VOI. GAN L2 provided the lowest dose uncertainties compared with the other methods. The PBM presented the highest dose uncertainties. Figure E2 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049) displays the systematic dose uncertainties (ME) of each method along the DVHs by VOI. The GAN L2 and U-Net L2 presented the lowest ME (in absolute value). The MEs of these methods were not significantly different from a null distribution along the DVH. The PBM, GAN PL, and U-Net PL provided the

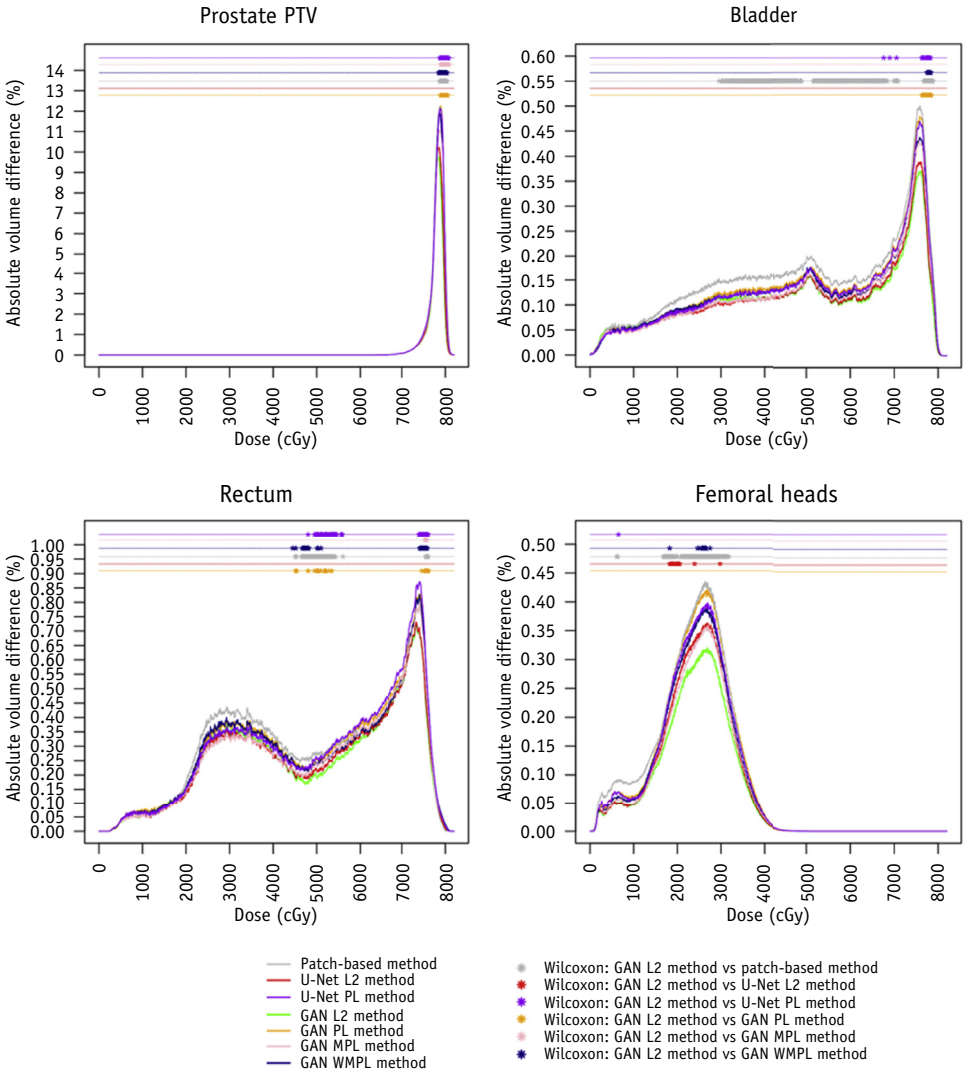

Fig. 3. Dose uncertainties (mean absolute error) for all pseudo-CT generation methods along the entire dose volume histogram (DVH) for the prostate Planning Target Volume (PTV), bladder, rectum, and femoral heads. The dose uncertainty is defined as the mean absolute DVH differences between the reference CT and the pCT corresponding to each method. Permutation tests were used to compare the absolute DVH differences of the generative adversarial network (GAN) L2 method to those of the other methods. *Significant differences ($P \leq .05$). *Abbreviations*: U-Net L2 = U-Net using a L2 loss; U-Net PL = U-Net using a single-scale perceptual loss (layer 7); GAN L2 = generative adversarial network using a L2 loss; GAN PL = generative adversarial network using a single-scale perceptual loss (layer 7); GAN MPL = generative adversarial network using a multiscale perceptual loss; GAN WMPL = generative adversarial network using a weighted multiscale perceptual loss.

highest ME (in absolute value). Table 2 lists the mean doses to target volume and organs-at-risk and dose uncertainties (MAE) and systematic dose uncertainties (ME) for specific DVH points. The GAN L2 and U-Net L2 showed the lowest MAE and ME. No statistically significant differences were found between MAE of GAN PL and U-Net PL.

Table 3 displays the mean gamma and gamma pass rate values calculated from the CT_{ref} and pCT dose distributions for each method. The highest mean gamma values were found for the U-Net L2 and GAN L2. The lowest gamma-pass rate and highest mean gamma values were found for the PBM.

Figure E3 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049) illustrates the pCTs, dose distributions, and gamma maps obtained from a patient.

Discussion

A total of 6 DLMs for pelvis pCT generation from MRI were investigated and compared with a PBM. Several

Table 2 Reference dose values, dose uncertainties (MAE), and systematic dose uncertainties (ME) for each pseudo-CT generation method for each volume of interest

Volumes of interest	Prostate CTV		Prostate PTV		Rectum			Bladder			Femoral heads	
Dosimetric endpoints	$D_{99\%}$ (cGy)	D_{mean} (cGy)	$V_{95\%}$ (%)	D_{mean} (cGy)	V_{70Gy} (%)	D_{max} (cGy)	D_{mean} (cGy)	V_{50Gy} (%)	D_{max} (cGy)	D_{mean} (cGy)	V_{30Gy} (%)	D_{mean} (cGy)
Reference CT values	7628 ± 50	7869 ± 52	97.1 ± 1.4	7816 ± 47	7.5 ± 3.0	7331 ± 166	3603 ± 277	22.4 ± 11.5	7784 ± 101	2951 ± 981	11.8 ± 6.5	1992 ± 249
Dose uncertainties (MAE)												
Patch-based method	39 ± 24*	36 ± 22*	0.6 ± 0.6	35 ± 20*	0.5 ± 0.9	48 ± 58	19 ± 15*	0.2 ± 0.1	32 ± 22*	12 ± 10*	0.3 ± 0.3*	7 ± 6*
U-Net method												
L2	31 ± 31*	29 ± 24*	0.6 ± 0.5	28 ± 23	0.5 ± 0.5	45 ± 45	15 ± 14	0.1 ± 0.1	26 ± 26	9 ± 10	0.3 ± 0.3*	6 ± 5*
PL	38 ± 23*	35 ± 19*	0.6 ± 0.6	35 ± 17*	0.6 ± 0.8	53 ± 65*	18 ± 14*	0.2 ± 0.1	30 ± 19	10 ± 9	0.3 ± 0.2	7 ± 5*
GAN method												
L2	28 ± 26	26 ± 24	0.6 ± 0.5	26 ± 22	0.5 ± 0.8	45 ± 59	15 ± 13	0.1 ± 0.1	25 ± 23	9 ± 9	0.2 ± 0.2	5 ± 5
PL	38 ± 24*	36 ± 21*	0.6 ± 0.6	35 ± 19*	0.5 ± 0.8	50 ± 65	18 ± 15*	0.2 ± 0.1	31 ± 19	11 ± 9*	0.3 ± 0.2	7 ± 5
MPL	34 ± 22*	32 ± 19	0.6 ± 0.6	32 ± 17	0.5 ± 0.8	48 ± 63	16 ± 13	0.1 ± 0.1	28 ± 19	10 ± 8	0.3 ± 0.2	6 ± 5
WMPL	36 ± 22*	34 ± 20*	0.6 ± 0.5	33 ± 18*	0.5 ± 0.8	50 ± 64	18 ± 14*	0.2 ± 0.1	29 ± 19	10 ± 9	0.3 ± 0.2	7 ± 5*
Systematic dose uncertainty (ME)												
Patch-based method	-16 ± 43*	-12 ± 41	-0.3 ± 0.8*	-13 ± 39*	-0.3 ± 0.8*	-31 ± 69*	-12 ± 21*	-0.1 ± 0.2	-11 ± 37	-5 ± 15*	-0.1 ± 0.4	-2 ± 9*
U-Net method												
L2	1 ± 40	5 ± 38	-0.1 ± 0.8	3 ± 36	-0.2 ± 0.9	-17 ± 73.3	-3 ± 21	0.0 ± 0.2	5.4 ± 36	1 ± 13	0.0 ± 0.3	1 ± 8
PL	-20 ± 40*	-15 ± 37*	-0.3 ± 0.8*	-16 ± 36*	-0.4 ± 0.9*	-36 ± 76*	-11 ± 21*	0.0 ± 0.2*	-9.6 ± 34	-3 ± 13*	-0.1 ± 0.3	-3 ± 8*
GAN method												
L2	1 ±38	6 ± 35	-0.1 ± 0.8	4 ± 34	-0.2 ± 0.9	-16 ± 73	-3 ± 20	0.0 ± 0.2	6 ± 34	0 ± 13	0.0 ± 0.3	1 ± 7
PL	-22 ± 40*	-17 ± 38*	-0.3 ± 0.8*	-17 ± 36*	-0.4 ± 0.9*	-36 ± 74*	-11 ± 21*	-0.1 ± 0.2*	-12 ± 34*	-4 ± 14*	-0.2 ± 0.4*	-4 ± 8*
MPL	-14 ± 39*	-10 ± 36	-0.3 ± 0.8*	-11 ± 35	-0.3 ± 0.9*	-29 ± 74*	-8 ± 20*	-0.0 ± 0.2	-7 ± 33	-2 ± 13	-0.1 ± 0.3	-2 ± 7
WMPL	-13 ± 40	-9 ± 39	-0.2 ± 0.8	-9 ± 37	-0.3 ± 0.9*	-31 ± 75*	-8 ± 21*	0.0 ± 0.2	-5 ± 35	-2 ± 14	-0.1 ± 0.3	-2 ± 8

Abbreviations: CTV = clinical target volume; PTV = planning target volume; ME = mean error; MAE = mean absolute error; GAN = generative adversarial network; CT = computed tomography; pCT = pseudo computed tomography; DVH = dose–volume histogram; U-Net L2 = U-Net using a L2 loss; U-Net PL = U-Net using a single-scale perceptual loss (layer 7); GAN L2 = generative adversarial network using a L2 loss; GAN PL = generative adversarial network using a single-scale perceptual loss (layer 7); GAN MPL = generative adversarial network using a multiscale perceptual loss; GAN WMPL = generative adversarial network using a weighted multiscale perceptual loss.

The mean values of DHV points are reported for the reference CT. The dose uncertainty is defined as the mean absolute DVH differences between the DVH calculated from the reference CT and those obtained from the pCTs. The systematic dose uncertainty is defined as the mean DVH differences between the DVH calculated from the reference CT and those obtained from the pCTs.

* The Wilcoxon test was used, first to compare the dose uncertainty (MAE) of the GAN with L2 loss to those of the other methods, and second, to compare the systematic dose uncertainty (ME) of the methods to a null distribution. Significant differences were considered at $P \leq .05$.

†The Wilcoxon test was also used to compare the dose uncertainties (MAE) of the GAN with perceptual loss to those of the U-Net with perceptual loss. Significant differences were considered at $P \leq .05$. Notice no significant differences were found between MAE from the GAN with perceptual loss to those from the U-Net with perceptual loss.

hyperparameters of the DLMs were optimized according to imaging endpoints (Appendix 4, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). Compared with the CT_{ref}, the pCTs generated by DLMs and PBM provided overall low dose uncertainties, thereby making them clinically acceptable for MRI-based prostate dose planning (Fig. 2). Regarding dose accuracy and calculation time, in comparison with PBM, DLMs appear particularly promising for clinical use. Among DLMs, the most accurate methods are GAN L2 and U-Net L2 (Table 2, Figs. 2 and 3, and Fig. E2, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049).

Deep learning has been used for pCT generation from MRI exclusively in the brain[23,25,26,57] and pelvis.[27,29,48,64-66] In the pelvis, 4 deep learning architectures have been used: fully convolutional network,[65] deep embedding convolutional neural network,[66] U-Net,[48,64] and GAN architecture without perceptual loss.[27,29] Imaging and dose endpoints have been considered to evaluate these methods within the scope of radiation therapy. All 6 studies evaluated the imaging endpoints in cohorts ranging from 15 to 39 patients, among which Arabi et al[48] used the same cohort of patients than used in the present study. In the entire pelvis, the MAEs were 42.4 HU[65] and 42.5 HU[66] when fully convolutional network and deep embedding convolutional neural network architectures were used, respectively. Using a U-Net architecture, the MAEs were 30 HU[64] and 32.7 HU.[48] Using a GAN architecture, the MAEs were 60 HU[27] and 39.0 HU.[29] Although the comparison can only be indirect, our proposed GAN L2 and U-Net L2 DLM compared favorably with an MAE value of 34.1 HU and 34.4 HU, respectively.

Only 4 studies in the literature evaluated the dose uncertainties: 3 in the pelvis[27,48,64] and 1 in the brain,[26] considering various dosimetric endpoints. In the pelvis, the mean dose uncertainties reported using U-Net and GAN DLMs were lower than 0.2% and 0.5% in all the VOIs.[27,48,64] Our mean dose uncertainties with GAN DLMs appear comparable (Table 2). In the literature, the reported mean gamma pass-rates were 98%[64] and 95%[48] with a 1%/1 mm criteria (in 2D), and 95% with a 2%/2 mm criteria (in 3D).[27] In comparison, we obtained a higher gamma pass-rate (99%) with our GAN and U-Net DLMs (Table 3).

In our study, compared with the PBM, our GAN and U-Net DLMs provided lower imaging uncertainties, with the lowest for GAN L2 and U-Net L2 (Table 1). The perceptual loss in U-Net and GAN did not decrease the HU

Table 3 Mean gamma and gamma pass-rate calculated from the reference CT and pseudo-CT dose distributions according to each method

			Gamma pass-rate (%)	Mean gamma	Gamma pass-rate (%)	Mean gamma
			1%/1 mm, 10% low dose threshold		1%/1 mm, 30% low dose threshold	
Methods used to generate pseudo-CT	Patch-based method		98.7 ± 1.4*	0.47 ± 0.20*	99.5 ± 1.3	0.40 ± 0.16*
	U-Net methods	L2	99.2 ± 1.0	0.39 ± 0.17	99.5 ± 1.5	0.33 ± 0.19
		PL	99.3 ± 0.8	0.42 ± 0.13*,†	99.8 ± 0.6	0.37 ± 0.15*
	GAN methods	L2	99.1 ± 1.0	0.39 ± 0.16	99.6 ± 1.3	0.32 ± 0.18
		PL	99.3 ± 0.9*	0.41 ± 0.15	99.7 ± 0.9	0.38 ± 0.16*
		MPL	99.2 ± 0.8	0.40 ± 0.14	99.7 ± 0.9	0.35 ± 0.15
		WMPL	99.3 ± 0.8*	0.40 ± 0.13	99.6 ± 1.1	0.36 ± 0.16*

Abbreviations: CT = computed tomography; U-Net L2 = U-Net using a L2 loss; U-Net PL = U-Net using a single-scale perceptual loss (layer 7); GAN L2 = generative adversarial network using a L2 loss; GAN PL = generative adversarial network using a single-scale perceptual loss (layer 7); GAN MPL = generative adversarial network using a multiscale perceptual loss; GAN WMPL = generative adversarial network using a weighted multiscale perceptual loss.

Values are mean ± standard deviation

* The Wilcoxon test was used to compare the gamma values of the GAN with L2 loss to those of the other methods. Significant differences were considered at $P \leq .05$.

† The Wilcoxon test was also used to compare the gamma values of the GAN with perceptual loss to those of the U-Net with perceptual loss. Significant differences were considered at $P \leq .05$.

uncertainty. This may be explained by the choice of our evaluation metric (HU difference, required within a dose calculation perspective), and not considering image quality metrics (universal image quality index[67]) such as peak signal-to-noise ratio, normalized mutual information,[68] structural SIMilarity,[69] visual information fidelity,[70] and learned perceptual image patch similarity[47,71] used in computer vision applications. These image quality metrics were not considered in this study as they are not relevant for dose evaluation.

Although the perceptual loss does not seem to provide any advantage for dose calculation, this loss function may be relevant for other image processing tasks like segmentation and registration within a CBCT-based IGRT. Moreover, for the bone, the addition of an adversarial term tends to decrease the imaging uncertainty in the GAN.

Considering all the methods, the largest uncertainties were observed for the bone (up to 144 HU for MAE), which are related to the highest HU values in the bone (345 HU, Table E1, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). For the rectum, large uncertainties were also observed (up to 78 HU for MAE, Table 1), potentially related to the difference in gas pockets between the MRI and CT_{ref}. However, all these methods seemed to incorrectly reproduce the real air pockets (when they were present both on CT and MRI), as illustrated in Figure E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049; sagittal views). This issue could be explained by the complex detection of air pockets with the T2 MRI and lack of variability of air pockets in the training cohort.

GAN PL and GAN L2 provided significantly lower imaging uncertainties (MAE) than U-Net PL and U-Net L2, respectively. GAN L2 and U-Net L2 presented the lowest dose uncertainties (MAE) (Table 2 and Fig. 3) without any systematic dose uncertainties (ME) (Table 2 and Fig. E2, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). Nevertheless, these results appeared more robust with the adversarial term of the GAN discriminator loss function (Appendix 5, available online at https://doi.org/10.1016/j.ijrobp.2019.08.049). In our previous study that compared the BDM, ABM, and PBM, PBM was found to be the most accurate pCT generation method. Figure E4 (available online at https://doi.org/10.1016/j.ijrobp.2019.08.049) compares the 9 strategies in the whole series of patients (BDM, ABM, PBM, and the 6 DLMs). This figure confirms that GAN L2 and U-Net L2 are the most accurate methods, and ABM and BDM are the least accurate. Overall, the dose uncertainties of the pCTs of each method are small and unlikely to be clinically relevant in terms of local control and toxicity.

Our study presents some limitations. First, before the learning process, nonrigid registration was used to align pelvic anatomies between MRI and CT_{ref}, with the intrinsic uncertainties linked to the deformable image registration algorithm. However, we previously quantified these geometric uncertainties in reference 20 by calculating the Dice scores before registration ($CT_{initial}$ vs MRI) and after registration (CT_{ref} vs MRI) for the prostate, seminal vesicles, bladder, and rectum volumes. We found that all Dice scores were significantly improved by the nonrigid registration ($P \leq .05$). Furthermore, these registrations did not correct the gas volatility in the digestive structures. The dose uncertainties related to rectal variations were quantified in our previous study using the PBM.[20] The gas correction (gas inside the pCT was deleted and replaced by the gas from the CT_{ref}) yielded a significant lowest dose uncertainty for the rectum between V15 Gy and V25 Gy.

Second, we investigated only the T_2-weighted MRI sequences. DLMs may be sensitive to variations in MRI, and other MR sequences could have been used. Because of the relative low number of patients, the optimization was performed with only 1 of the 3 draws. No test set was therefore used, potentially exposing our optimization to a bias. Even if the pCTs generated by DLMs and PBM provided overall low dose uncertainties, an outlier analysis should be performed on an independent and large enough data set. The GAN DLM was trained with 2D axial slices and not with 3D images because of the GPU memory limitations. To overcome this issue, 3D patches could have been used during the training, however, at the expense of the contextual information inclusion. Indeed, small 3D patches ($32 \times 32 \times 32$ or $64 \times 64 \times 64$) ignore the global anatomic information, as opposed to a 2D slice. In addition, 3D architectures are often shallow compared with 2D architectures.[29] Another solution could be brought by the generation of pCTs from individual 2D axial, sagittal, and coronal slices fused together, adding 30 more seconds once the networks are trained. Finally, other emerging deep learning architectures such as the cycle-GAN, which may have allowed us to overcome some intraindividual coregistration issues, could have been investigated.

Conclusions

To generate pCT for MRI-based prostate dose planning, DLMs appear to be particularly promising for clinical practice owing to the low dose uncertainty and fast calculation time. The U-Net and GAN DLMs with L2 loss function provide the lowest dose uncertainties. These MRI approaches in prostate cancer radiation therapy, which do not require any CT, could thereby improve the accuracy of VOI delineation and can also be used for (re)planning in the MRI-LINAC workflow.[72]

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