Original paper

Dose distribution correction for the influence of magnetic field using a deep convolutional neural network for online MR-guided adaptive radiotherapy

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ABSTRACT

Purpose: This study aimed to develop a deep convolutional neural network (CNN)-based dose distribution conversion approach for the correction of the influence of a magnetic field for online MR-guided adaptive radiotherapy.

Methods: Our model is based on DenseNet and consists of two 2D input channels and one 2D output channel. These three types of data comprise dose distributions without a magnetic field (uncorrected), electron density (ED) maps, and dose distributions with a magnetic field. These data were generated as follows: both types of dose distributions were created using 15-field IMRT in the same conditions except for the presence or absence of a magnetic field with the GPU Monte Carlo dose in Monaco version 5.4; ED maps were acquired with planning CT images using a clinical CT-to-ED table at our institution. Data for 50 prostate cancer patients were used; 30 patients were allocated for training, 10 for validation, and 10 for testing using 4-fold cross-validation based on rectum gas volume. The accuracy of the model was evaluated by comparing 2D gamma-indexes against the dose distributions in each irradiation field with a magnetic field (true).

Results: The gamma indexes in the body for CNN-corrected uncorrected dose against the true dose were $94.95\% \pm 4.69\%$ and $63.19\% \pm 3.63\%$, respectively. The gamma indexes with 2%/2-mm criteria were improved by 10% in most test cases (99.36%).

Conclusions: Our results suggest that the CNN-based approach can be used to correct the dose-distribution influences with a magnetic field in prostate cancer treatment.

1. Introduction

Over the previous few decades, image-guided radiotherapy (IGRT) techniques have significantly improved dose convergence for targets and dose reduction for normal tissues, owing to the ability to visualize the patients' anatomical structures during each treatment fraction [1,2]. The available imaging techniques, such as on-board kV/MV planar imaging, in-room computed tomography (CT), cone beam CT, and ultrasoundography have been used for current IGRT, resulting in great clinical improvements, as mentioned above. However, magnetic resonance

imaging (MRI) offers the several advantages, such as high visualization of lesions and normal tissues, imaging without additional irradiation, high quality and acquisition speed, geometric flexibility to acquire images in 2D/3D, and access to functional imaging. In recent years, the researches in MR-guided radiotherapy have been studied intensively owing to these advantages, with the aim of improving the treatments, such as online adaptive radiation treatment, target tracking without fiducial markers, and target margin reductions [3,4]. Recently, integrated radiotherapy and MRI imaging systems, such as the combination of an MRI scanner with either a linear accelerator (MRI-linac) or a

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cobalt-60 therapy system, are commercially available. These systems have been enthusiastically researched and rapidly introduced into clinical practice for various cancer regions [5–8].

Although online MR-guided adaptive radiotherapy offers several advantages, there are several challenges for clinical use. One of the challenges is that the dose distribution in a magnetic field is influenced by the Lorentz force on the secondary electrons. These dose perturbations (e.g., electron return effect [9], electron streaming effect [10]) can cause unexpected dose distributions, such as hot and/or cold spots owing to anatomical changes (e.g., gas pockets) during inter/intra treatment fractions. Conventional dose calculation algorithms have not shown the ability to cope with the transport of charged particles in a magnetic field. There is a need for sophisticated dose calculation algorithms, such as the stochastic Monte Carlo method or a deterministic grid-based Boltzmann solver, for solving the linear Boltzmann transport equation [11,12]. Although they have the ability of accurate dose calculation, they are extremely time-consuming and involve a high calculation costs for online MR-guided adaptive radiotherapy that may generate a new treatment plan for each fraction. Other challenges involve the independent dose verification prior to patient treatment that is needed each time the treatment plan is replanned. Therefore, an efficient secondary dose check method is needed. Graves et al commissioned and investigated the RadCalc software (Lifeline Software Inc., Tyler, USA), a widely used secondary point dose calculator for patient quality assurance, for use with the Elekta Unity MRI-linac [13]. They reported that although modest improvements were possible with the modification of the standard model to account for the effect of a magnetic field (67.3% vs. 96.5% mean 5%/5-mm gamma passing rate); the modification could introduce unacceptable risk and increase the verification time.

In recent years, deep learning has been significantly investigated, and several researches on medical imaging and radiotherapy, including tumor and organ segmentation [14,15], artifact reduction [16], image registration [17], response-to-treatment and toxicity prediction [18,19] among others have been conducted. Among these, the task of dose distribution estimation using deep learning is a popular research topic. Nguyen et al developed a deep convolutional neural network (CNN)-based model for dose prediction by using the regions of interest (ROI) of the targets and organs [20,21]. Dong et al introduced a CNN-based approach to convert from a dose distribution using a low-cost algorithm to highly accurate dose distributions with the absence of a magnetic field [22]. Therefore, CNN has the potential to perform dose estimation tasks.

In this paper, we proposed a novel deep convolutional neural network (CNN)-based dose distribution conversion approach to enable the simple correction of the influence of a magnetic field to allow

accurate and efficient online MR-guided adaptive radiotherapy. It may be possible to correct the influence of magnetic field in the dose distribution using CNN approach that consists of large number of convolution filters and has the potential to directly learn the behavior of secondary electrons in magnetic field. To our knowledge, this is the first study to develop and evaluate a CNN model for correcting the dose distribution in the presence of a magnetic field.

2. Materials and methods

2.1. Overall scheme

Fig. 1 presents our proposed framework for dose-distribution conversion approach to correct the influence of the magnetic field. First, we performed the planning with a magnetic field and made the calculations in the same conditions except for the absence of a magnetic field. Second, we pre-processed the patients' data for our model training and validation; the doses were normalized, based on the assessments with the magnetic field; CT images were converted to electron density (ED) map and normalized. Third, we trained and validated our dose conversion CNN model with 4-fold cross-validation, and then created 4 trained CNN models. Fourth, we used the trained CNN models to estimate the doses with the magnetic field and then combined and averaged the 4 estimated doses to achieve the CNN-corrected dose. Finally, we evaluated our proposed approach by performing a comparison between the CNN-corrected dose distributions and the corresponding dose distributions with the magnetic field against uncorrected dose distributions (without a magnetic field).

2.2. Patient information

This retrospective analysis was approved by our institutional review board. Total 50 patients with prostate cancer who were treated with IMRT used in conventional Linac from 2009 to 2018 were selected from the database of our institution. All patients for whom complete data were available were (e.g., contour data) included in the analyses. All the patients had clinical stage T1-3N0M0 prostate cancer and were classified as being high risk as per the National Comprehensive Cancer Network definitions (www.nccn.com). They had fiducial markers for the patient setup and a urethral catheter to identify the urethra with planning CT image acquisition [23]. In the study cohort, 40 and 10 patients were elected for training/validation and testing, respectively, with stratified 4-fold cross-validation based on the rectum gas volume. The median gas volumes of the datasets were 0.16 cc, 0.15 cc, 0.14 cc, 0.15 cc, and 0.13 cc. There were no significant differences in the rectum gas among the five datasets, using Wilcoxon signed-rank test.

Fig. 1. Schematic diagram of the workflow.

2.3. Data preparation

In this study, we used the Monaco version 5.4 (Elekta AB, Stockholm, Sweden) as the treatment planning system (TPS) corresponding to Unity (Elekta, Stockholm, Sweden), a 1.5 T MRI scanner with a 7-MV flattening filter free (FFF) linac. All the patients were manually re-planned with fifteen-field IMRT instead of volumetric modulated arc therapy (VMAT); the photon energy was 7-MV flattening filter free (FFF), and the gantry angles were 0°, 24°, 48°, 72°, 96°, 120°, 144°, 168°, 192°, 216°, 240°, 264°, 288°, 312°, and 336°. VMAT with a magnetic field was unavailable in the current Monaco version 5.4. CT images were acquired using GE Light Speed RT16 (GE Healthcare, Wisconsin, USA). X-ray tube voltage was set to 120 kV. Spatial resolution in the axial plane was 512×512 . Pixel size in the axial plane ranged from about 0.88 to 1.17 mm. The slice thickness was set to 2.5 mm. The clinical target volume (CTV) consisted of only the prostate, assuming low-risk prostate cancer, and the planning target volume (PTV) was obtained by expanding the CTV in the left–right and the anterior directions by 1.0 cm, in the superior–inferior direction by 0.6 cm, and in the posterior direction by 0.5 cm. The clinical CT-to-electron density (ED) curve was used for dose calculation in our institution. All the planes were optimized in the presence of a 1.5-T transverse magnetic field using the GPU Monte Carlo dose (GPUMCD) in Monaco version 5.4 by sparing the rectum, bladder, and femoral heads as per the department low-risk prostate cancer radiotherapy treatment protocol, based on the QUANTEC data [24]. Furthermore, the doses were calculated under the same conditions except, the absence of the magnetic field. The dose calculations were performed with a statistical uncertainty of 2% and grid spacing of 2 mm per plan. In order to reduce the inaccuracy in dose calculation, the electron density values of the fiducial markers and the artifacts of the markers were replaced 1.884 and 1.062 g/cm³ following our clinical workflow, respectively.

In order to build consistency in the accuracy of dose distribution, body structures, defined as the dose calculation region, were contoured with semi-automatic contouring, and immobilizers were not included in the body structures. Structures of couch components and RF body coil were replaced for planning CT couch as per our institutional clinical workflow. They were assigned the electron densities corresponding to the material. It is noteworthy that the dose calculation region was defined as only the patient's body, structures of couch components, and RF body coil.

All data (i.e., dose distributions with or without magnetic field, CT images) were pre-processed for data types in the input or output of our CNN model. The dose distributions in each irradiation field without magnetic field were normalized 0 to 1, and the dose distributions in each irradiation field with magnetic field were normalized 0 to 1; thereafter, they were multiplied by a maximum dose with magnetic field or the

maximum dose without magnetic field because the relationships between dose intensities with and without the magnetic field were maintained. The CT values were converted to electron density map as per our institution's clinical CT-to-ED curves and by replacing the fiducial markers and the artifacts of the markers to obtain the ED maps. The ED maps were rescaled as per the range of the CT-to-ED curves by using the following scale: −1000 HU is 0, 4000 HU is 1. The ED maps were down-sampled to the equivalent voxel size of dose distribution (i.e., $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$). All the pre-processed data were cropped to 160×224 , and the values for outside the body were replaced to 0. All the three-dimensional (3D) datasets were divided to 2D axial slices with > 30% of the maximum dose without the magnetic field.

2.4. Model architecture

Fig. 2 shows the architecture of our proposed model for dose conversion. This model is based on DenseNet [25], without the down-sampling function. Our hypothesis for the absence of down-sampling function was that the features of local region are more useful than those of global region in the dose-distribution conversion task because the Lorentz force only affects the local regions. This model consists of two two-dimensional (2D) inputs and one 2D output, each with a size of 160×224 . The input channels have the data for the dose distribution in each irradiation field without a magnetic field and ED map. The output channel represents the data for the dose distribution in each irradiation field with a magnetic field, corresponding to the input channels. First, $128 \ 3 \times 3$ convolution filters with 1×1 stride followed by batch normalization [26] and parametric rectified linear unit (PReLU) [27] combined the input data and extract features. Second, the output feed through subsequent 3 dense blocks corresponded to the electron radius for the patient's anatomical structure in the transverse magnetic field. The dense blocks consist of 4 convolutions and each connection part. The convolution part consists of $64 \ 3 \times 3$ convolution filters with 1×1 stride after $64 \ 1 \times 1$ convolution filters with 1×1 stride called “Bottleneck layer” to improve the computational efficiency [28]. The connection part involves the combined features extracted by previous and next convolution parts followed by batch normalization and PReLU. Third, the output is processed with $64 \ 1 \times 1$ convolution filters with 1×1 stride; thereafter, this convoluted output was combined with the ED map to reflect the patient's anatomical geometry. Fourth, the output was processed with $64 \ 3 \times 3$ convolution filters with 1×1 stride, $32 \ 3 \times 3$ convolution filters with 1×1 stride and $16 \ 3 \times 3$ convolution filters with 1×1 stride in order, followed by batch normalization and PReLU in all the convolution processes. Finally, the output was processed with a single 1×1 convolution filters with 1×1 stride followed by ReLU [29], as the estimated dose distribution was corrected with the influence of magnetic field.

Fig. 2. The architecture of our proposed CNN model for correcting the influence of the magnetic field.

2.5. Training/validation

Our models were trained by using Nadam ($\text{lr} = 0.0001$, $\beta_1 = 0.9$, $\beta_2 = 0.999$, $\text{decay} = 0.004$) as the optimization algorithm [30]. The mean squared error (MSE) between the pixels of the training dataset was used as the loss function. The model parameters were initialized with He-normal [27]. The maximum epoch was 100, and batch size was 16. We used the framework of Keras 2.2.4 (backend TensorFlow 1.13.1). Computation was performed using NVIDIA Quadro RTX 8000.

2.6. Evaluation

After training/validation process, 4 CNN models were obtained with best epoch (i.e., smallest validation loss). We entered the test data comprising the 10 unseen patients for training for each trained model. The 4 outputs in the same slice for each patient were combined and averaged without replacement (CNN-Corrected). Gamma indexes [31] in patients' body, 3-mm thickness skin, and evaluation ROI expanded rectum in the all directions by 3-mm (rectum + 3-mm) were calculated in order to evaluate the agreement of dose distribution by comparing the dose without the magnetic field (uncorrected dose) with the dose distributions with a magnetic field, defined as the true dose. The gamma indexes based on the global gamma analysis were calculated at 1%/1-mm, 2%/2-mm, and 3%/3-mm, based on $> 10\%$ of the maximum value of the true dose. The indexes were calculated using the MATLAB codes (<https://github.com/mwgeurts/gamma>) freely available, which is based on the formulation in a report described above. Moreover, the MSEs were calculated for the patients' body by comparing the dose without the magnetic field. We used the Wilcoxon signed-rank test to determine significant differences between the CNN-corrected to true and uncorrected to true gamma index using the MATLAB R2018a software.

3. Results

Fig. 3 shows an example of the training and validation loss function from one of the folds and MSEs comparing the CNN-corrected and uncorrected dose distribution against true dose in the patients' body. The average loss $\pm$ one standard deviation for training and validation between all the folds with the best epoch were $4.17 \times 10^{-5} \pm 2.20 \times 10^{-6}$ and $4.91 \times 10^{-5} \pm 7.62 \times 10^{-6}$, respectively. In the training process, each epoch takes ~ 23 min. In the estimation process, each 2D dose distribution takes ~ 80 msec. The MSEs between CNN-corrected and uncorrected dose in the patients' body against true dose were $9.61 \times 10^{-5} \pm 4.99 \times 10^{-5}$ and $6.53 \times 10^{-4} \pm 2.72 \times 10^{-4}$, respectively. Our CNN model significantly estimated the MSEs via a comparison with the uncorrected dose. Figs. 4 and 5 show an example of dose distribution

comparison and ED map via the bone and rectum gas region, respectively. In addition, they present the profiles of true, CNN-corrected dose, uncorrected dose, and errors against true dose between CNN-Corrected and uncorrected dose. In Fig. 4, although the errors of CNN-corrected and uncorrected doses are within $\pm 5\%$ except in the skin region, the error of CNN-corrected dose is less than that of the uncorrected dose in the skin and bone regions. In Fig. 5, the errors of CNN-corrected and uncorrected doses are within $\pm 5\%$, except in the skin and surrounding rectum gas. However, the error of CNN-corrected dose is less than uncorrected dose in the regions surrounding the skin and rectum gas. Fig. 6 shows the violin plots of the gamma indexes in the body, the skin and the rectum +3-mm between the CNN-corrected and uncorrected dose against the true dose. For the body, the 3%/3-mm passing rate improved from 84.26 ± 2.55 between uncorrected and true dose to 98.92 ± 2.58 between the CNN-corrected and true dose, from 63.19 ± 3.63 to 94.95 ± 4.69 at 2%/2 mm, and from 27.18 ± 4.03 to 73.10 ± 7.61 at 1%/1 mm. The gamma passing rates with 2%/2 mm criteria were improved by 10% in most test cases (99.36%). For the skin, the 3%/3 mm passing rate improved from 79.79 ± 11.59 between uncorrected and true dose to 97.31 ± 4.57 between CNN-Corrected and true dose, from 61.75 ± 13.28 to 93.28 ± 6.92 at 2%/2 mm, and from 37.45 ± 14.44 to 79.15 ± 10.66 at 1%/1 mm. The gamma passing rates with the 2%/2 mm criteria were improved by 10% in most test cases (94.67%).

4. Discussion

The focus of this study was on the development and evaluation of a CNN-based dose-distribution conversion approach for simple correction of the influence of a magnetic field to enable accurate and efficient online MR-guided adaptive radiotherapy. In order to evaluate our proposed approach, we calculated the MSEs and gamma indexes for different settings between the CNN-corrected and uncorrected doses against doses with a magnetic field. Our analyses revealed that our proposed approach had good agreement with true doses and improved by 10% in most test cases (99.36%) for gamma passing rate at 2%/2-mm criteria against the uncorrected dose, showing its potential as the correction ability for dose distribution with a magnetic field and an improved approach for online MR-guided adaptive radiotherapy.

As shown in Fig. 6, average gamma passing rates were 94.95% at 2%/2-mm criteria and 98.92% at 3%/3-mm criteria, compared with the CNN-corrected dose against the true dose. Aubin et al developed and evaluated a discontinuous finite element space-angle treatment of the linear Boltzmann transport equation for accurate estimation of the effects of magnetic fields [11]. They reported greater than 98.9% of all points analyzed passed the 2%/2 mm gamma criteria against Monte Carlo dose calculation algorithm for two field strengths (0.5 and 3 T) and

Fig. 3. An example of a training and validation loss from one of the folds (left). The blue and red curves indicate training and validation loss, respectively. The boxplots of the mean squared errors between the CNN-corrected and uncorrected doses against the true dose (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. An example with relatively good agreement between the CNN-corrected and true dose distributions. For dose profiles, solid, broken, and dotted lines indicate doses with magnetic field (true), CNN-corrected/uncorrected dose, and the errors between true and CNN-corrected/uncorrected doses, respectively. Red and blue curves indicate CNN-corrected and uncorrected doses, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 5. An example with relatively poor agreement between the CNN-corrected and true dose distributions. For dose profiles, solid, broken, and dotted lines indicate doses with magnetic field (true), CNN-corrected/uncorrected dose, and the errors between true and CNN-corrected/uncorrected doses, respectively. Red and blue curves indicate CNN-corrected and uncorrected doses, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 6. Violin plots of the two-dimensional gamma passing rates for the regions in the body, skin and the rectum + 3-mm.

orientations tested using an inhomogeneous 3D slab geometry phantom consisting of water, bone and air or lung. Although our results were less accurate than those reported by Aubin (94.95% vs. 98.9% at 2%/2 mm criteria), we used the clinical images of the patients with relatively more complex geometry than theirs. Moreover, Graves et al investigated the utility and performance of the RadCalc software for Elekta Unity MRI-linac [13]. They reported that the average gamma passing rate was 96.5% at 5%/5 mm criteria, compared to the true dose through

artificially shifting of jaws and multi-leaf collimator positions to account for the dosimetric shift owing to the magnetic field. Although there were several different points, as mentioned above, such as datasets, plan settings, and dose calculation methods, our results, using a simple correction method, may be comparable or superior in accuracy to the reports by Aubin and Graves. Our results show that our proposed CNN-method has the potential to be useful for online MR-guided adaptive radiotherapy workflow, especially for independent dose calculation and

secondary dose check.

One of the advantages of MR-guided adaptive radiotherapy in the pelvic region is to adapt to anatomical changes (e.g., a different rectum and bladder filling, presence or absence of rectal gas) in the duration of radiotherapy treatment [32,33]. Thus, high accuracy of dose-distribution calculation for the boundary of air surfaces easily influenced by a magnetic field especially is required. However, as shown in Figs. 4 and 5, there is a tendency that the skin and surrounding rectal gas cannot be corrected better than the homogeneous medium in this study. Therefore, it is assumed that there are mainly two factors. First, one of these factors is the dataset bias. In this study, the correction accuracy surrounding the rectal gas was relatively low. Although no significant differences in the rectal gas volume were observed among five groups (i.e., four training/validation and one test dataset), the present model would not train the pattern of rectal gas adequately because the number of cases including rectal gas in dataset was limited. Moreover, the influence of the gas is not in every case a problem but could be one if major changes of rectum filling with gas occur. However, for a case of multi-directional plan such as this study and VMAT in the region with relatively homogeneity structures like pelvis, the influence of this error may be small clinically. Second, one of these factors is the 2D data format of input and output. The influence of dose distribution with a magnetic field is mainly electron return effect (ERE) and electron streaming effect (ESE), and these influences are 3D phenomenon. Because of these influences, dose distributions are affected by secondary electrons caused by multiple slices along the axial direction. Thus, although the dataset had relatively enough data size for the skin, the present approach based on 2D CNN would not have been enough to correct these effects in the skin. This error may have a clinical effect in the regions with large air volume, such as the lung and abdomen. Further investigation to improve the performance would be required.

The present approach can potentially generate treatment plans with magnetic field directly by applying the dose distributions optimized in the absence of a magnetic field. Therefore, treatment plans for MR-linacs can be generated without Monte Carlo simulation but with only kernel-based dose calculation algorithms. Thus, the planning time and cost can be potentially reduced when replanning is required. Moreover, the plan optimization would be more efficient because differences between dose distributions with and without magnetic field might be smaller by introducing the present approach in the beam fluence optimization process.

We suggest the potential of the present approach based on CNN for conversing dose distributions with a magnetic field. However, even if the same model architecture is used, the performance of deep learning-based approach depends on the method and the dataset quality generally. Although training parameters were used, i.e., 16 as patch size, Nadam as optimizer, and 0.0001 as learning rate in this study, these training parameters may be optimized. Moreover, anatomical variations (e.g., presence or absence of rectal gas) in dataset affects the performance of the CNN-based model. Although we performed with stratified fourfold cross-validation based on the rectal gas volume, the dataset quality and quantity may be insufficient to prevent the influence of this anatomical problem. To generalize the present approach, further investigation would be required.

Although our results showed the potential of CNN in correcting the influence of the magnetic field, there are certain limitations of this study. First, we used the GPUMCD algorithm as the base dose calculation method. Dong et al introduced a deep learning-based strategy to obtain highly accurate dose plan (a grid size of $1.25 \times 1.25 \times 1.25$ mm using Acuros XB (AXB) algorithm) by transforming from a dose distribution calculated using a low-cost algorithm (a grid size of $5 \times 5 \times 5$ mm using Analytical Anisotropic algorithm (AAA)) [22]. They reported that the average gamma passing rates at 2%/2-mm criteria improved from 66% to 86% between the up-sampled AAA and CNN against AXB under different beam settings (i.e., iso-center location, field sizes and gantry angles) and regions (i.e., brain, thorax, abdomen and pelvis) without a

magnetic field. In spite of the presence of a magnetic field, our results (94.95 ± 4.69 at 2%/2 mm criteria) were superior to their findings. The differences might be attributable to the variations in the base dose calculation methods, such as algorithms and grid size (GPUMCD vs. AAA). We plan to further investigate other calculation algorithms with less accuracy and computation costs (e.g., collapsed cone convolution (CCC), Clarkson's method). Second, we studied only patients with prostate cancer with the fixed treatment plan configuration (e.g., beam energy, beam number, beam angles, and strength of magnetic field). Although our results showed the potential of improving the calculation accuracy for these plan configuration and region, the treatment plan is relatively similar because of the relatively stable anatomy. Thus, whether our proposed method is useful for other types of treatment plans and regions remains unclear. Further investigation to validate the feasibility for other types of treatment plans and anatomical regions would be required. Third, in this study, we used and evaluated only one kind of model framework based on DenseNet and configuration of the model's hyper-parameters (e.g., kernel size, kernel numbers, and layer numbers). DenseNet is a popular CNN model, and popular hyper-parameters such as the kernel size (e.g., 3×3 convolution kernel) was used. Although our model had a good potential correcting influence of a magnetic field, there is a possibility that the model architecture and these hyper-parameters were not optimal. Further investigation to evaluate the performance of other popular CNN model architecture (e.g., U-Net [34]) using in medical physics would be required.

5. Conclusions

In this study, we proposed and validated a CNN-based dose-distribution conversion approach correcting the dose distribution with a magnetic field. Our results suggest that deep learning can be applied to the correction of the dose distribution influences with a magnetic field in the prostate cancer treatment.

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Declaration of Competing Interest

There is no conflict of interest with regard to this manuscript.

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