Technical Note: Deriving ventilation imaging from 4DCT by deep convolutional neural network

Yuncheng Zhong

Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Yevgeniy Vinogradskiy

Department of Radiation Oncology, University of Colorado Denver, Aurora, CO, USA

Liyuan Chen

Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Nick Myziuk

Department of Radiation Oncology, Beaumont Health System, Royal Oak, MI, USA

Richard Castillo

Department of Radiation Oncology, Emory University, Atlanta, GA, USA

Edward Castillo and Thomas Guerrero

Department of Radiation Oncology, Beaumont Health System, Royal Oak, MI, USA

Steve Jiang and Jing Wang^{a)}

Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA

(Received 6 August 2018; revised 20 December 2018; accepted for publication 22 January 2019; published 15 April 2019)

Purpose: Ventilation images can be derived from four-dimensional computed tomography (4DCT) by analyzing the change in HU values and deformable vector fields between different respiration phases of computed tomography (CT). As deformable image registration (DIR) is involved, accuracy of 4DCT-derived ventilation image is sensitive to the choice of DIR algorithms. To overcome the uncertainty associated with DIR, we develop a method based on deep convolutional neural network (CNN) to derive ventilation images directly from the 4DCT without explicit image registration.

Methods: A total of 82 sets of 4DCT and ventilation images from patients with lung cancer were used in this study. In the proposed CNN architecture, the CT two-channel input data consist of CT at the end of exhale and the end of inhale phases. The first convolutional layer has 32 different kernels of size $5 \times 5 \times 5$, followed by another eight convolutional layers each of which is equipped with an activation layer (ReLU). The loss function is the mean-squared-error (MSE) to measure the intensity difference between the predicted and reference ventilation images.

Results: The predicted images were comparable to the label images of the test data. The similarity index, correlation coefficient, and Gamma index passing rate averaged over the tenfold cross validation were 0.880 ± 0.035 , 0.874 ± 0.024 , and 0.806 ± 0.014 , respectively.

Conclusions: The results demonstrate that deep CNN can generate ventilation imaging from 4DCT without explicit deformable image registration, reducing the associated uncertainty. © 2019 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.13421>]

Key words: 4DCT lung ventilation imaging, convolutional neural network, lung functional imaging

1. INTRODUCTION

Functional imaging is emerging as a potentially important tool in the planning and evaluation of lung cancer radiotherapy plans. Lung function avoidance has been applied in intensity-modulated radiation therapy (IMRT) planning to limit dose delivered to well-functioning lung parts.^{1,2} Conventional methods to obtain lung ventilation images include nuclear medicine ventilation–perfusion (VQ) scans, positron emission tomography (PET), single-photon emission computer tomography (SPECT), or hyperpolarized He-3 magnetic resonance imaging (MRI).^{3–5} Despite providing functional images, these methods suffer some shortcomings

including requiring contrast agent administration, longer processing time. In addition, other factors, such as availability and cost, also limit their applications. Therefore, a more convenient method for lung functional imaging is needed in wider clinical applications.^{6–8}

A four-dimensional computed tomography (4DCT)-based method has been developed to obtain ventilation images. As 4DCT images are easily accessible during radiation treatment planning, 4DCT-based ventilation images can be obtained at virtually no additional monetary or dosimetric cost. The method has been validated and evaluated for its ability to generate functional images compared with conventional methods with promising results. Applications of these 4DCT-based

ventilation images in radiation therapy have been reported.^{5,6,9–16} Lung ventilation images from 4DCT images are calculated according to either Hounsfield unit (HU) changes or regional expansion and contraction of lung volumes. In the method involving HU changes, the temporally resolved reconstructed images at distinct phases within the respiratory cycle are registered, and the HU values are compared based on a simple model of lung tissue as a linear combination of air and “tissue” components to infer the respiratory volume changes and ventilation images. In the method involving regional expansion and contraction, ventilation images are obtained using the Jacobian of the deformable image registration (DIR) displacement field,¹⁰ without explicit accounting of the underlying registered CT image values. Hybrid approaches have also been proposed, whereby the Jacobian determinant is regionally scaled by the ratio of registered HU.¹⁷

The aforementioned approaches rely on the DIR between images at different respiratory phases. Because selecting DIR algorithms affects the stability of the process,^{18,19} the accuracy of 4DCT-derived ventilation images is sensitive to the choice of the DIR algorithms. The difference in the Dice similarity coefficients varies up to 50% when different DIR algorithms were used.²⁰ An improved method to derive ventilation images from 4DCT is desired to improve the robustness of the 4DCT ventilation calculation process.

Deep learning methods have been successfully applied to the field of medical imaging, improving image processing,²¹ registration,^{22,23} denoising,^{24,25} and classification.²⁶ The deep convolutional neural network (CNN) method extracts features from images and generates model-specific parameters.^{27–34} CNN can reveal the latent features that are not easily discovered by conventional image-processing methods. Successful applications of the deep CNN method on image registration and motion tracking make it a promising approach for ventilation imaging generation from 4DCT. In this work, we propose a deep CNN-based method to derive ventilation images directly from the 4DCT without explicit image registration to overcome the uncertainty associated with selecting an accurate DIR algorithm. The proposed method uses 4DCT images as input and the known ventilation images as labeled data for training. Upon training completion, we evaluated the results by quantitatively comparing the predicted results with the reference ventilation images.

2. MATERIALS AND METHODS

2.A. Data and preprocessing

We used a supervised machine learning scheme that needs input data and label data to train the models. The input data in our study are 4DCT-reconstructed images at the end of inhalation and exhalation stages. The selection of the end of inhalation and exhalation was to utilize the maximum expansion of the lung to predict the ventilation imaging. This strategy has been adopted in most of previously developed 4DCT-based ventilation.^{7,14,35} These same two phases were

also used to generate the labeled 4DCT-based ventilation image. The output as the label data are the ventilation images. The workflow and process are illustrated in Fig. 1. In this preliminary study, ventilation images obtained using the DIR and HU change method were used as the labeled data for training.¹¹ Data for this study were generated as part of prospective functional avoidance clinical trial (NCT02528942). A total of 82 sets of 4DCT and ventilation images from lung cancer patients were used for the study. The majority (72%) of patients had stage III disease and 44% of patients had accompanying chronic obstructive pulmonary disease. Images were preprocessed and randomly divided into training and testing groups.

The lungs were segmented on the 4DCT images at the end of inspiration and the end of expiration phases. The segmented images were further cropped to include only the lungs in order to reduce the input image size and computation burden during the model training. Images were segmented using the NIH-CIDI Lung Segmentation tool, which was based on fuzzy connectedness segmentation using graph cut.³⁶ The segmented lung images were adjusted manually as needed to eliminate other structures, such as heart.

2.B. Convolutional neural network architecture

The CNN architecture for generating ventilation images based on 4DCT images is shown in Fig. 2. The proposed architecture is composed of one input layer, six convolution layers, and one final prediction layer. Images at the end of inhalation and exhalation are utilized as input. In each convolutional layer, a set of learnable small spatially kernels are included to capture local features for each pixel in the images. Zero padding is used in each convolution layer to preserve the output size of each feature map. Additionally, each

Fig. 1. The overall process of the proposed method. 4DCT images were segmented and cropped and formed two-channel input (dashed box). The label data (colored) were cropped to the same dimensions. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 2. The convolutional neural network architecture used in the study.

convolution layer in the proposed architecture is followed by an activation layer that is controlled by an activation function. The activation function that we used in this work is rectifier linear units (ReLU). ReLU has been shown to achieve more efficient gradient propagation and more efficient computation than the logistic sigmoid and hyperbolic tangent activation function. The final prediction layer in the proposed CNN model is composed of one convolutional layer and one ReLU layer. We used ReLU instead of sigmoid to avoid gradient vanishing. The range of the predicted values is within the interval of $[0,100]$.

In this study, a total of 82 sets of 4DCT and ventilation images from lung cancer patients were used. We implemented the experiments in tenfold cross validation; each time we used 90% 4DCT sets (around 72 4DCT sets) as the training dataset to train the proposed CNN model. Each voxel in the 4DCT image can be treated as a training sample since we are solving an end-to-end problem. Thus, the training sample utilized in the training process is $72 \times 220 \times 300 \times 116$ ($\sim 5 \times 10^8$), which is much greater than the total number ($\sim 5 \times 10^5$) of parameters embedded in the proposed CNN model.

The type of filters in the proposed CNN architecture is not fixed. By training the CNN model, the value of each element in each filter is updated based on the back propagation from the loss function. The filters in the first several layers attempt to learn the low-level features and the filters in the later several layers attempt to combine the low-level features to high-level features for the final prediction. The number and size of filters in each layer are adjusted based on performance of the validation dataset. We chose 32 features in the layer 1 and 16 features in the layer 2 and so on. The filter size in the first layer is larger because it needs to process the input data from both channels. We tuned the filter sizes and found the size of 5 gave the best results.

To train the proposed CNN model, several key steps are described as follows:

- (1) Initialization: Initialization of the network weights will affect the convergence of the network. For the

proposed CNN model, we used the Xavier initialization method,³⁷ which assigns the network weights from a Gaussian distribution with zero mean and a variance of $1/N$ where N specifies the number of input neurons. Through Xavier initialization, the variance of input and output for each layer is the same to avoid gradients vanishing or explosion in back propagation and to ensure activation functions can work normally.

- (2) Loss function: The loss function that we used to train the proposed CNN model is mean-squared-error (MSE) between the predicted image and label image.
- (3) Optimization algorithm: We used Adam optimization algorithm which works well in practice and compares favorably to other stochastic optimization methods, to train the proposed CNN model in our experiments. It computes individual adaptive learning rates for different parameters from estimates of first and second moments of the gradients. The initial learning rate and maximum epoch for training in this work are set as 8×10^{-5} and 50, respectively.

We conducted tenfold cross validation of the patient data to validate model optimization. Data were randomly divided into ten groups with eight or nine patients within a group. Datasets from nine groups were assembled for model training and the remaining group was used to test the predicted model. During the training process, we use 90% of training data to train the model and 10% as validation data to select the best model. We then used this selected model to evaluate its performance on the testing data. After each group has been used as the testing data, we obtained ten sets of results. The average quantities over these ten sets were then calculated.

2.C. Evaluation

Upon completion of training, the model was applied to the independent test dataset with eight or nine patients, depending on the random selection from the ten groups. The predicted ventilation images were compared with the reference images generated with the standard DIR-based algorithm. We

used the structure similarity index (SSIM) and correlation coefficient (Spearman's r) as metrics to evaluate the comparison of the predicted and labeled images.^{38,39} The structure similarity is described as

$$SSIM(x, y) = [l(x, y)]^\alpha \cdot [c(x, y)]^\beta \cdot [s(x, y)]^\gamma \quad (1)$$

with

$$l(x, y) = \frac{2\mu_x\mu_y + C_1}{\mu_x^2 + \mu_y^2 + C_1}$$

$$c(x, y) = \frac{2\sigma_x\sigma_y + C_2}{\sigma_x^2 + \sigma_y^2 + C_2}$$

$$s(x, y) = \frac{\sigma_{xy} + C_3}{\sigma_x\sigma_y + C_3}$$

where $l(x, y)$, $c(x, y)$, $s(x, y)$ represent comparison of luminance, contrast, and structure, respectively; μ_x , μ_y , σ_x , σ_y , and σ_{xy} represent mean, standard deviation, and cross-covariance, respectively; C_1 , C_2 represent the square of 1% and 3% of the dynamic range value, respectively; $C_3 = C_2/2$; α , β , γ represent the weighting for each comparison, respectively, and were set to 1 in our study.

The correlation coefficients were computed according to the following equation:

$$\rho(x, y) = \frac{1}{N-1} \sum_{i=1}^N \left(\frac{x_i - \mu_x}{\sigma_x} \right) \left(\frac{y_i - \mu_y}{\sigma_y} \right) \quad (2)$$

where μ_x , μ_y , σ_x , σ_y are defined above; N indicates the number of samples; x_i , y_i indicate individual samples.

The gamma index passing rate was defined as the ratio of the voxels with the gamma index not greater than 1.⁴⁰ The gamma index was defined as:

$$\Gamma(x_i, y_j) = \sqrt{\frac{r^2(x_i, y_j)}{\Delta d^2} + \frac{\delta^2(x_i, y_j)}{\Delta I^2}} \quad (3)$$

$$r(x_i, y_j) = |x_i, y_j|$$

$$\delta(x_i, y_j) = I_j(y_j) - I_i(x_i)$$

where x_i and y_j represent the coordinates of voxels on the two images; $I(y_j)$ and $I(x_i)$ represent the intensity at the voxels on the two images; $r(x_i, y_j)$ is the distance between the two voxels; Δd and ΔI are the criterion of distance-to-agreement and intensity difference. While the gamma index is usually used for comparing doses, it could be used to compare intensities. We set the criterion to be 5% and 5 mm for intensity and distance-to-agreement, respectively.

3. RESULTS

The MSE values converges with epochs in the training and the relative errors are plotted (Fig. 3). The relative errors for the test cases using the trained model range from 5.6% to 9.7%, with the mean relative error of 7.6%. The training stops after 50 epochs to ensure completion of the minimization process. The visual similarity between the predicted and the label images is shown in Fig. 4 for a representative axial slice

FIG. 3. The relative error as a function of the number of epochs during the training. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. Comparison of the prediction (top) and the label data (bottom). [Color figure can be viewed at wileyonlinelibrary.com]

(patient CU26B). These images demonstrate good correspondence in their morphology and intensity distribution. The comparison of other testing data shows similar results (Fig. 5). In general, the predicted images [Fig. 5(c)] of the testing data are similar to those of the label data [Fig. 5(d)] in terms of shape and intensity distribution with local deviations. The overlay of the ventilation images with the chest images provides an overview of the lung ventilation images [Fig. 5(e)].

The SSIM, correlation coefficients, and gamma index passing rate calculated from tenfold cross validations were listed in Tables I, II, and III, respectively. The overall average values were 0.880 ± 0.035 , 0.874 ± 0.024 , and 0.806 ± 0.014 for SSIM, correlation coefficients, and gamma index passing rate, respectively.

4. DISCUSSIONS AND CONCLUSION

In this work, lung motion and HU changes between the end of inhalation and end of exhalation phases are explored by a CNN model to generate ventilation images. Although the explicit model format is unknown, CNN provides the

FIG. 5. Columns (a) and (b) are the input data. Column (c) and (d) are the prediction and the label data, respectively. Column (e) combined prediction with the chest computed tomography. Each row is for one set of patient data. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE I. SSIM values between predicted and label images for tenfold cross validation.

Case	1	2	3	4	5	6	7	8	9	Average $\pm$ SD
f1	0.973	0.942	0.948	0.895	0.959	0.948	0.858	0.947		0.934 ± 0.038
f2	0.967	0.973	0.900	0.986	0.878	0.822	0.883	0.909		0.915 ± 0.057
f3	0.831	0.850	0.914	0.885	0.833	0.933	0.900	0.875		0.878 ± 0.038
f4	0.914	0.791	0.939	0.880	0.887	0.913	0.924	0.915		0.895 ± 0.046
f5	0.892	0.791	0.937	0.866	0.883	0.903	0.917	0.913		0.888 ± 0.045
f6	0.906	0.837	0.908	0.905	0.867	0.930	0.936	0.929		0.902 ± 0.034
f7	0.663	0.875	0.803	0.732	0.892	0.728	0.883	0.917		0.812 ± 0.094
f8	0.889	0.778	0.852	0.912	0.874	0.905	0.759	0.901		0.859 ± 0.059
f9	0.862	0.872	0.894	0.794	0.890	0.838	0.901	0.898	0.788	0.860 ± 0.044
f10	0.843	0.782	0.949	0.825	0.867	0.890	0.790	0.885	0.870	0.856 ± 0.052

parameters and network structures to predict ventilation images using the end of inspiration and the end of expiration CT images as input. This model integrates image motion, morphology, and HU changes. The proposed method does not involve the calculation of DIR, which helps reduce the uncertainty associated with the DIR algorithms.

In this preliminary study, labeled images are the ventilation images calculated using the DIR and HU change methods because of the limitation to access direct functional

ventilation images. Any error in the labeled imaged will affect the training results. Under the current condition, the best accuracy achieved is limited by the accuracy of the label data that is obtained with DIR-based 4DCT ventilation. Nevertheless, with this proof of the concept study, we will evaluate other lung function imaging modalities such as SPECT, MRI with hyperpolarized He-3, or nuclear medicine ventilation-perfusion images as labeled data for the training in future study. The accuracy is expected to improve with these

TABLE II. Correlation values between predicted and label images for tenfold cross validation.

Case	1	2	3	4	5	6	7	8	9	Average $\pm$ S.D.
f1	0.881	0.849	0.891	0.880	0.959	0.939	0.916	0.949		0.908 ± 0.039
f2	0.850	0.763	0.912	0.702	0.927	0.910	0.942	0.918		0.866 ± 0.088
f3	0.847	0.915	0.901	0.945	0.892	0.934	0.938	0.888		0.908 ± 0.033
f4	0.695	0.805	0.729	0.853	0.918	0.930	0.955	0.872		0.845 ± 0.095
f5	0.696	0.797	0.682	0.854	0.915	0.910	0.951	0.876		0.835 ± 0.101
f6	0.836	0.807	0.846	0.839	0.832	0.920	0.948	0.958		0.873 ± 0.059
f7	0.758	0.891	0.830	0.840	0.910	0.832	0.826	0.948		0.854 ± 0.059
f8	0.899	0.869	0.792	0.908	0.896	0.934	0.863	0.890		0.881 ± 0.042
f9	0.878	0.852	0.889	0.910	0.908	0.865	0.898	0.893	0.855	0.883 ± 0.022
f10	0.893	0.867	0.949	0.839	0.863	0.907	0.874	0.921	0.847	0.884 ± 0.036

TABLE III. Gamma index passing rate values between predicted and label images for tenfold cross validation.

Case	1	2	3	4	5	6	7	8	9	Average $\pm$ SD
f1	0.683	0.809	0.761	0.897	0.848	0.902	0.796	0.792		0.811 $\pm$ 0.072
f2	0.849	0.809	0.767	0.795	0.830	0.740	0.856	0.822		0.809 $\pm$ 0.040
f3	0.695	0.883	0.794	0.890	0.793	0.902	0.893	0.749		0.825 $\pm$ 0.078
f4	0.742	0.811	0.921	0.803	0.740	0.718	0.802	0.873		0.801 $\pm$ 0.070
f5	0.764	0.807	0.891	0.828	0.741	0.702	0.834	0.861		0.803 $\pm$ 0.064
f6	0.782	0.746	0.721	0.839	0.762	0.772	0.853	0.765		0.780 $\pm$ 0.045
f7	0.975	0.816	0.843	0.776	0.830	0.561	0.838	0.836		0.809 $\pm$ 0.116
f8	0.753	0.643	0.765	0.878	0.790	0.907	0.811	0.755		0.788 $\pm$ 0.082
f9	0.911	0.766	0.780	0.818	0.789	0.738	0.845	0.794	0.937	0.820 $\pm$ 0.067
f10	0.805	0.763	0.732	0.877	0.823	0.832	0.762	0.889	0.837	0.813 $\pm$ 0.053

TABLE IV. Comparison of the learning results using two phases and four phases input data. P2: input and label data obtained from two phases (end of inspiration and the end of exhalation, phases 0 and 5); P4: additional two phases (phases 4 and 9) included as input.

	SSIM	Corr	Gamma
P2	0.916	0.941	0.890
P4	0.875	0.901	0.857

new label data. The expanded validation will help demonstrate the potential robustness of the CNN model approach to calculating ventilation images. While the CNN-based approach investigated in this work can potentially overcome the uncertainty of DIR, the approach still relies on the image quality of 4DCT. Similar to DIR-based methods, artifacts in 4DCT can still affect the accuracy in derived ventilation image.⁴¹ Therefore, advanced 4DCT approaches that can mitigate sorting artifacts are desired to improved accuracy of 4DCT ventilation image.⁴²

The input data used in this study only contain two phases as the labeled images were generated from the same paired images. The proposed CNN-based method can be modified to incorporate other phases as input, especially when label data are the direct ventilation images. We preliminarily investigated the influence of the input data by including additional phases during the model training. Specifically, two additional phases (phases 4 and 9) are included as the input for the CNN model. The accuracy of predicted ventilation image with more respiration phases becomes worse based on the metrics listed in Table IV. The main cause of decreased prediction accuracy is that the labeled output ventilation images are obtained from two phases of 4DCT (end of inspiration and the end of expiration phases). This preliminary comparison study suggests that 4DCT-based ventilation images are phase dependent and the ventilation images from MRI or nuclear medicine are desired as the labeled images. With more appropriate labeled ventilation images, the influence of input containing more phases of 4DCT on the performance of CNN-based method will be investigated in a future study.

In summary, we have demonstrated the feasibility of using deep CNN to generate ventilation images from 4DCT. The predicted ventilation images after training show a high degree of similarity to the label data. With direct ventilation images as label data and more images from various phases as input, the method is expected to generate better prediction images.

ACKNOWLEDGMENTS

This work was partially supported by grant NIH R01CA200817 (YV, EC, RC, TG) and NIH R01 EB020366 (YZ, LC, JW). We thank Dr. Damiana Chiavolini for helping with the editing.

CONFLICTS OF INTEREST

The authors have no conflicts to disclose.

^{a)}Author to whom correspondence should be addressed. Electronic mail: jing.wang@utsouthwestern.edu.

REFERENCES

1. Lee E, Zeng J, Miyaoka RS, et al. Functional lung avoidance and response-adaptive escalation (FLARE) RT: multimodality plan dosimetry of a precision radiation oncology strategy. *Med Phys.* 2017;44:3418–3429.
2. Ireland RH, Tahir BA, Wild JM, Lee CE, Hatton MQ. Functional Image-guided radiotherapy planning for normal lung avoidance. *Clin Oncol.* 2016;28:695–707.
3. Siva S, Hardcastle N, Kron T, et al. Ventilation/perfusion positron emission tomography-based assessment of radiation injury to lung. *Int J Radiat Oncol Biol Phys.* 2015;93:408–417.
4. Siva S, Devereux T, Ball DL, et al. Ga-68 MAA perfusion 4D-PET/CT scanning allows for functional lung avoidance using conformal radiation therapy planning. *Technol Cancer Res Treatm.* 2016;15:114–121.
5. Kipritidis J, Siva S, Hofman MS, Callahan J, Hicks RJ, Keall PJ. Validating and improving CT ventilation imaging by correlating with ventilation 4D-PET/CT using Ga-68-labeled nanoparticles. *Med Phys.* 2014;41:12.
6. Yamamoto T, Kabus S, von Berg J, Lorenz C, Keall PJ. Impact of four-dimensional computed tomography pulmonary ventilation imaging-based functional avoidance for lung cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;79:279–288.

7. Guerrero T, Sanders K, Castillo E, et al. Dynamic ventilation imaging from four-dimensional computed tomography. *Phys Med Biol*. 2006;51:777–791.
8. Reinhardt JM, Ding K, Cao K, Christensen GE, Hoffman EA, Bodas SV. Registration-based estimates of local lung tissue expansion compared to xenon CT measures of specific ventilation. *Med Image Anal*. 2008;12:752–763.
9. Vinogradskiy Y, Koo PJ, Castillo R, et al. Comparison of 4-dimensional computed tomography ventilation with nuclear medicine ventilation-perfusion imaging: a clinical validation study. *Int J Radiat Oncol Biol Phys*. 2014;89:199–205.
10. Castillo R, Castillo E, McCurdy M, et al. Spatial correspondence of 4D CT ventilation and SPECT pulmonary perfusion defects in patients with malignant airway stenosis. *Phys Med Biol*. 2012;57:1855–1871.
11. Vinogradskiy Y, Jackson M, Schubert L, et al. Assessing the use of 4DCT-ventilation in pre-operative surgical lung cancer evaluation. *Med Phys*. 2017;44:200–208.
12. Vinogradskiy YY, Castillo R, Castillo E, Chandler A, Martel MK, Guerrero T. Use of weekly 4DCT-based ventilation maps to quantify changes in lung function for patients undergoing radiation therapy. *Med Phys*. 2012;39:289–298.
13. Tahir BA, Van Holsbeke C, Ireland RH, et al. Comparison of CT-based lobar ventilation with He-3 MR imaging ventilation measurements. *Radiology*. 2016;278:585–592.
14. Ding K, Bayouth JE, Buatti JM, Christensen GE, Reinhardt JM. 4DCT-based measurement of changes in pulmonary function following a course of radiation therapy. *Med Phys*. 2010;37:1261–1272.
15. Ding K, Cao KL, Fuld MK, et al. Comparison of image registration based measures of regional lung ventilation from dynamic spiral CT with Xe-CT. *Med Phys*. 2012;39:5084–5098.
16. Patton TJ, Gerard SE, Shao W, Christensen GE, Reinhardt JM, Bayouth JE. Quantifying ventilation change due to radiation therapy using 4DCT Jacobian calculations. *Med Phys*. 2018;45:4483–4492.
17. Li M, Castillo E, Zheng X-L, et al. Modeling lung deformation: a combined deformable image registration method with spatially varying Young's modulus estimates. *Med Phys*. 2013;40:081902.
18. Miura H, Ozawa S, Nakao M, et al. Impact of deformable image registration accuracy on thoracic images with different regularization weight parameter settings. *Phys Med-Eur J Med Phys*. 2017;42:108–111.
19. Castillo E, Castillo R, Vinogradskiy Y, Guerrero T. The numerical stability of transformation-based CT ventilation. *Int J Comput Assist Radiol Surg*. 2017;12:569–580.
20. Latifi K, Forster KM, Hoffer SE, et al. Dependence of ventilation image derived from 4D CT on deformable image registration and ventilation algorithms. *J Appl Clin Med Phys*. 2013;14:4247–4247.
21. Ker J, Wang LP, Rao J, Lim T. Deep learning applications in medical image analysis. *IEEE Access*. 2018;6:9375–9389.
22. Fu M, Wu WM, Hong XF, et al. Hierarchical combinatorial deep learning architecture for pancreas segmentation of medical computed tomography cancer images. *BMC Syst Biol*. 2018;12:56.
23. Wu GR, Kim MJ, Wang Q, Gao YZ, Liao S, Shen DG. Unsupervised deep feature learning for deformable registration of MR brain images. In: Sakuma I, Barillot C, and Navab N, Eds. *Medical Image Computing and Computer-Assisted Intervention - Miccai 2013*, Pt II. vol. 8150; 2013:649–656.
24. Badretale S, Shaker F, Babyn P, Alirezaie J. Fully convolutional architecture for low-dose CT image noise reduction. In: 2017 International Conference on Artificial Intelligence Applications and Technologies. vol. 261; 2017. IOP.
25. Wang CM, Elazab A, Jia FC, Wu JH, Hu QM. Automated chest screening based on a hybrid model of transfer learning and convolutional sparse denoising autoencoder. *Biomedical Engineering Online*. 2018;17:63.
26. Feng YQ, Zhang L, Yi Z. Breast cancer cell nuclei classification in histopathology images using deep neural networks. *Int J Comput Assist Radiol Surg*. 2018;13:179–191.
27. Yun J, Yip E, Gabos Z, Wachowicz K, Rathee S, Fallone BG. Neural-network based autocontouring algorithm for intrafractional lung-tumor tracking using Linac-MR. *Med Phys*. 2015;42:2296–2310.
28. Laurent R, Henriot J, Salomon M, et al. Simulation of lung motions using an artificial neural network. *Cancer Radiother*. 2011;15:123–129.
29. Laurent R, Henriot J, Salomon M, Saugeat M, Gschwind R, Makovicka L. Respiratory lung motion using an artificial neural network. *Neur Comput Appl*. 2012;21:929–934.
30. Seregni M, Pella A, Riboldi M, Orecchia R, Cerveri P, Baroni G. Real-time tumor tracking with an artificial neural networks-based method: a feasibility study. *Phys Med-Eur J Med Phys*. 2013;29:48–59.
31. Bukovsky I, Homma N, Ichiji K, et al. A fast neural network approach to predict lung tumor motion during respiration for radiation therapy applications. *Biomed Res Int*. 2015;13:489679.
32. Jurkovic IA, Stathakis S, Papanikolaou N, Mavroidis P. Prediction of lung tumor motion extent through artificial neural network (ANN) using tumor size and location data. *Biomed Phys Eng Express*. 2016;2:12.
33. Teo TP, Ahmed SB, Kawalec P, et al. Feasibility of predicting tumor motion using online data acquired during treatment and a generalized neural network optimized with offline patient tumor trajectories. *Med Phys*. 2018;45:830–845.
34. Sun WZ, Jiang MY, Ren L, Dang J, You T, Yin FF. Respiratory signal prediction based on adaptive boosting and multi-layer perceptron neural network. *Phys Med Biol*. 2017;62:6822–6835.
35. Castillo R, Castillo E, Martinez J, Guerrero T. Ventilation from four-dimensional computed tomography: density versus Jacobian methods. *Phys Med Biol*. 2010;55:4661–4685.
36. Mansoor A, Bagci U, Foster B, et al. CIDI-Lung-Seg: a single-click annotation tool for automatic delineation of lungs from CT scans. In: *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. New York: IEEE; 2014:1087–1090.
37. Glorot X, Bengio Y. Understanding the difficulty of training deep feed-forward neural networks. In: *Proceedings of the Thirteenth International Conference on Artificial Intelligence and Statistics*; 2010:249–256.
38. Wang Z, Bovik AC, Sheikh HR, Simoncelli EP. Image quality assessment: from error visibility to structural similarity. *IEEE Trans Image Process*. 2004;13:600–612.
39. Spearman C. The proof and measurement of association between two things. *Int J Epidemiol*. 2010;39:1137–1150.
40. Li H, Dong L, Zhang LF, Yang JN, Gillin MT, Zhu XR. Toward a better understanding of the gamma index: investigation of parameters with a surface-based distance method. *Med Phys*. 2011;38:6730–6741.
41. Hegi-Johnson F, Keall P, Barber J, Bui C, Kipritidis J. Evaluating the accuracy of 4D-CT ventilation imaging: first comparison with Technegas SPECT ventilation. *Med Phys*. 2017;44:4045–4055.
42. Thomas D, Lamb J, White B, et al. A novel fast helical 4D-CT acquisition technique to generate low-noise sorting artifact-free images at user-selected breathing phases. *Int J Radiat Oncol Biol Phys*. 2014;89:191–198.