

# Random-Forest Model Prediction of Dose Distribution In Intensity Modulated Radiation Therapy (IMRT) Planning for Lung Cancer

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ARTICLE INFO	ABSTRACT
<p><b>Article type:</b> Original Paper</p> <hr/> <p><b>Article history:</b> Received: Mar 10, 2022 Accepted: Aug 21, 2022</p> <hr/> <p><b>Keywords:</b> Radiation Dose Prediction Instensity-Modulated Radiotherapy Machine Learning</p>	<p><b>Introduction:</b> Machine-learning models have been widely used to predict dose distribution in therapy planning such as Intensity Modulated Radiation Therapy (IMRT). Random-forest is one of the machine learning models which can reduce output bias by using the average value all of estimators.</p> <p><b>Material and Methods:</b> Planning data in Digital Imaging and Communications in Medicine (DICOM) format is exported to Comma Separated Values (CSV). Then, used to random-forest algorithm that will be trained using 7-fold validation and then the model will be evaluated with new data, i.e., data that the model has never seen before. The data evaluated were the parameters to obtain Homogeneity Index (HI) for the target organ, whereas the mean and max dose for organs at risk (OARs) were evaluated. Statistical analysis were also carried out to assess the significant difference between the predicted value and the true value.</p> <p><b>Results:</b> Random-forest was able to predict the true value with errors evaluated using Mean Absolute Error (MAE) on Planning Target Volume (PTV) features <math>D_2</math> (0.012), <math>D_{50}</math> (0.015) and <math>D_{98}</math> (0.018) as well as at OAR features (<math>D_{mean}</math> and <math>D_{max}</math>) of the right lung (0.104 and 0.228), left lung (0.094 and 0.27), heart (0.088 and 0.267), spinal cord (0.069 and 0.121) and (V95) Body (0.094). Based on the results of statistical tests, <math>p &gt; 0.05</math>, there is no significant difference between the two data.</p> <p><b>Conclusion:</b> Random-forest regressor is able to predict the dose value with the smallest difference in PTV features.</p>

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## Introduction

Based on data from the Global Burden of Cancer (GLOBOCAN) in 2020, lung cancer ranks 2nd in the world after breast cancer cases in women and is the number 1 killer of cancer cases. At the Asian level, lung cancer ranks first based on incidence and mortality rates [1]. Meanwhile, in Indonesia, lung cancer ranks third after breast cancer and cervical cancer, with data of 34,783 new cases [2].

Cancer treatment can be treated with surgery, anti-tumor drug therapy (chemotherapy, hormone therapy, and immunotherapy), and radiotherapy. The radiotherapy treatment technique is by utilizing high-energy ionizing radiation [3]. Radiotherapy treatment is divided into internal and external radiation. External radiotherapy, or External Beam Radiation Therapy (EBRT) is a therapy in which the radiation source is outside the target. One of the radiotherapy techniques used in EBRT is Intensity Modulated Radiotherapy (IMRT). This radiotherapy technique is equipped with Multi Leaf Collimators (MLCs) technology that can adjust to the size, shape, and location of the tumor [4].

Radiation therapy consists of a target volume covered by a planning target volume (PTV) and healthy organs around the tumor or organ at risk (OAR). The dose is delivered and is expected to be distributed maximally to the target volume and minimally to healthy organs. This IMRT technique is able to achieve this goal [4]. Before radiation treatment, it is necessary to do a dose calculation simulation called the Treatment Planning System (TPS). Although the dose calculation has been done computationally, the optimization in the planning process is still repeated to achieve the optimal dose distribution [5].

Many research have been conducted applying Artificial Intelligence (AI) to predict dose values [6] specifically, algorithms as well as machine learning (ML). By studying pre-existing data during the training step, the ML algorithm can be used to classify data or predict a value from it [7]. Organ shape (radiomics) and dose distribution (dosimomics) information are needed to train the ML model in radiation treatment planning [8].

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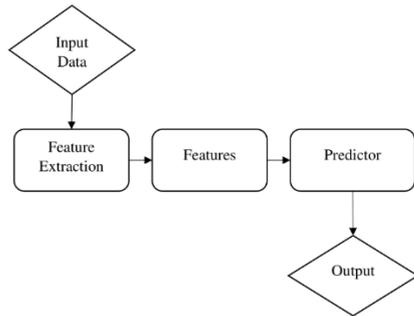


Figure 1. Algorithm of machine learning

The first supervised algorithm is one of several types of machine learning algorithms. This algorithm provides training data in the form of shapes, sizes, colors, etc., which have been attached or labeled to each piece of data. The best result of this study is that this algorithm can accurately predict the value in new data that has never been seen before. The second is the unsupervised algorithm, which has complete control over the results. It is, however, constrained by certain mechanisms of machine learning outcomes. In other words, a more educated machine will have a higher predictive value. The third type is the semi-supervised algorithm. This algorithm gives some labeled data and some unlabeled data. Labeled data will help learn unlabeled data so that the algorithm can develop its predictive ability. Figure 1 shows the problem solving algorithm in the machine learning process, where this process starts from input data in the form of input data to be processed. The next stage is data extraction, processing data information needed for prediction. Furthermore, the data that has been extracted is in the form of features (can be in the form of geometry or shape). And the last stage before getting the output is the process of predicting a value from the learning outcomes [7]. The method in this research study uses a supervised algorithm.

Random-forest (RF) is one of the ML models that uses a supervised learning algorithm, which was first introduced by Breiman et al. in 1984. Random-forest is a collection of decision trees (DTs) that number in the hundreds of thousands [9]. Each decision tree consists of decision nodes (DNs) and leaf nodes (LNs). Each decision node will evaluate the given input sample using a test function and will be forwarded to a different branch based on the features of the sample [10]. In DN, DT applies the Iterative Dichotomizer 3 (ID3) algorithm. This algorithm is applied to evaluate the input on each DN, which is mathematically written as [7]:

$$\text{Gain}(A) = H(A) - H(A|C) \tag{1}$$

where the value of "gain" measures the predicted value in A associated with C. H is the entropy calculated from the probability distribution of c discrete state (p<sub>1</sub>, p<sub>2</sub>,...p<sub>n</sub>).

$$H(A) = \sum_{n=1}^c -p_n \log_2 \frac{p_n}{2} \tag{2}$$

Tree progression will stop when all partitions or parameters have been used. However, this method can also overfit when the DT model continues to branch and grow to get a prediction result or a decision. This overfitting can be overcome by using the ensemble learning method. With this method, the ML model will create several of the same methods (in this case, the DTs method). Then from several DTs, the average value or the frequent value will be taken as the final decision value. This method is called random-forest. This method is divided into two random stages. The first stage is the bootstrapping stage, in which the training sample is chosen at random using resampling with replacement. Furthermore, the parameter attributes will be chosen and distributed at random in each LN [7], it showed in Figure 2.

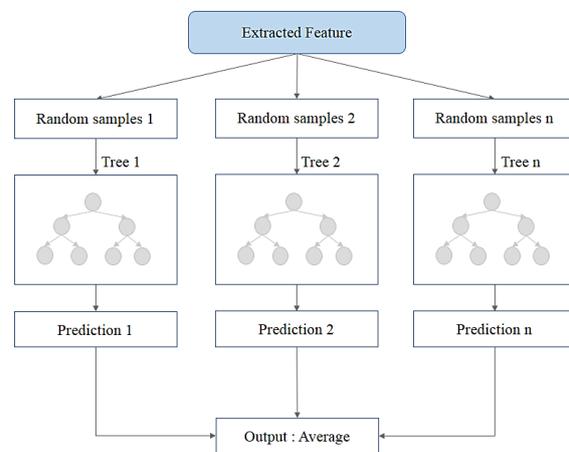


Figure 2. Algorithm of random-forest

To train a ML model, it needs to use both radiomics and dosiomics features. This can increase the predictive value compared to using only one feature (radiomics or dosiomics only) [11]. One of the ML models that can be used to predict a value from data is the random-forest model [7]. The validation method that can be used at the stage of training is k-fold validation, also known as cross validation to train models with prevent overfitting [12]. The goal of this study is to predict dose distribution quickly and reduce the trial and error process in planning therapy using the IMRT method, so that medical physicists can spend less time planning. Using this dose prediction method, medical physicists can accurately predict the dose of each target organ or healthy organ prior to conducting repeated trials during the therapy planning stage.

## Materials and Methods

### Data Collection

There are as many as 60 datasets about lung cancer patients who were treated with IMRT radiation therapy. This information came from the MRCCC Siloam Hospital Semanggi's Radiotherapy Installation,

specifically patient data from 2014 to 2021. The data is split into two sets, with the training set representing 70% of the entire data and the testing set representing 30% of the total data. Figure 3. shows an example of a database used for cases of right lung cancer. The blue contour represents the left lung organ, the light cyan represents the spinal cord, the soft cyan represents the right lung, the pink color represents the heart, and the red color represents the PTV organ.

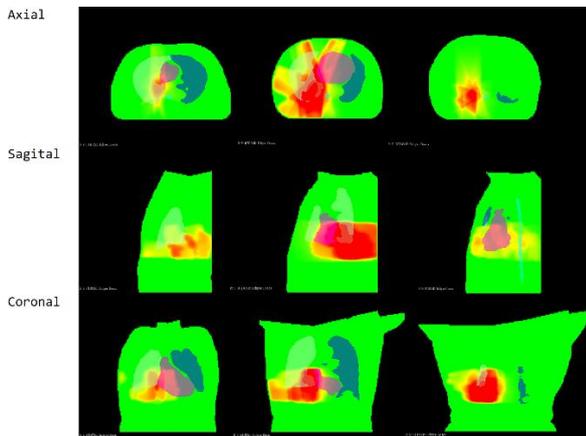


Figure 3. Example of IMRT planning database used; (left to right) axial : upper, middle, lower slice, sagittal : right side, middle, left side slice, Coronal : front, middle, rear slice

**Data Extraction**

The data was collected in the form of Digital Imaging and Communications in Medicine or DICOM-formatted patient planning data. The required data, such as Computed Tomography (CT) data of the patient, data structures contoured by the specialist oncology, and data distribution of the dose of the planned IMRT, cannot be processed directly in the program. Following that, the required data, such as CT data from the patient, data structures contoured by the doctor, and data distribution of the dose of the planned IMRT, must be extracted into feature radiomics and dosiomics and stored in formats such as Comma Separated Values (CSV).

**Radiomics**

Radiomics contain information about the shape of each organ that has been drawn on the CT image. This feature was extracted using the Pyradiomic tools [11] on 3D slicer 5.0. Radiomics are extracted from the gray scale CT image and organ contours drawn by a specialist [8]. The features of the organs used are target organs especially PTV and healthy organs or OAR especially right lung, left lung, heart and spinal cord.

**Dosiomics**

Dosiomics are features extracted from the dose distribution in the form of a dose volume histogram (DVH). Dosiomics itself is a new thing that has been used in the development of research in recent years that can increase the level of accuracy of a prediction [13]. The planning data used has a prescribed dose of 10-60

Gy. Extractable data from dosiomics will then be normalized based on the prescribed dose of each patient.

Although dosiomics obtains DVH information, the DVH curve does not include it. This is because dosiomics only provides information on volume covered by percentage of dose ( $V_x$ ) and dose in percentage of volume ( $D_x$ ) [14]. This study used the average dose ( $D_{mean}$ ) and maximum dose ( $D_{max}$ ) on OAR, as well as a dose of 2% ( $D_2$ ), a dose of 50% ( $D_{50}$ ) and a dose of 98% ( $D_{98}$ ) on PTV volume.

**Random-forest Regressor Model**

The Random-forest regressor is one of the ML models used to predict a value. The Random-forest itself is a collection of methods for decision tree, where each decision trees will provide a predictive value. The final result or output of this model is calculated by taking the average of all the predictions in the decision tree [15]. The random-forest algorithm can be seen in Figure 2 [16].

**Set Training**

Set training is divided into 2 stages, especially training and validation, which in total amounted to 70 percent of the total data. There are 42 data points at this stage to be trained using k-fold validation, with the number of k being 7-fold, which means every iteration there will be 36 data for training and 6 data for validation. The input sample can be expressed as X which contains m features ( $X = x_1, x_2, \dots, x_m$ ) while the output can be expressed as Y so that the training set can be expressed as  $S_n$  consisting of n observations. Mathematically it can be expressed as in equation (3) [10]:

$$S_n = \{(X_1, Y_1), (X_2, Y_2), \dots, (X_n, Y_n)\} \tag{3}$$

Each decision tree will perform data splitting to be forwarded to the decision node as a new input (X), which is repeated until it reaches the leaf node stage. The training process will be stopped if the specified maximum number has been reached or if the node contains the specified number of observations [10].

The output value of the random-forest  $\hat{Y}$  is expressed as obtained from the average value of decision trees, mathematically expressed as [10]:

$$\hat{Y} = \frac{1}{n} \sum_{i=1}^n \hat{Y}_i = \frac{1}{n} \sum_{i=1}^n \hat{h}(X, S_n^{O_i}) \tag{4}$$

where  $\hat{Y}_i$  is output  $i^{th}$  from tree ( $i = 1, 2, \dots, n$ ), n is the number of trees and  $\hat{h}(X, S_n^{O_i})$  is a function of prediction.

In this study, the radiomics feature  $X_{train}$ , which has been labeled by the dosiomics feature  $Y_{train}$ , will be the initial input to the random-forest model, which will be divided into each decision tree randomly. In this study, a decision tree is also called an estimator of 1000 ( $n = 1000$ ). This division method will allow some data to be studied repeatedly on several estimators so that this will reduce sensitivity to noise [10].

**Set Testing**

Set testing uses the remaining data or data that is not used at the training stage, training which is 30% of the total data, which is 18 data. This data is used to test the ML model that has been trained. Set testing itself is new data, or data that has never been seen by the model. Once a model is trained with the data  $X_{train}$  and  $Y_{train}$ , the model will be evaluated using the new data to provide input feature radiomics ( $X_{test}$ ) without giving the labeling feature ( $Y_{test}$ ). The model will calculate predictions ( $Y_{pred}$ ) based on the prediction function learned from the set testing stage, and the final result of the random-forest prediction is the average value of all estimators [10].

**K-Fold Validation**

K-fold validation, also called cross validation, is one of the methods used to divide data at the stage training set. The data will be divided by k equally. The number of k used in this study is 7 ( $k = 7$ ), which means that each data set will fold 1, 2, ...7. In the first set, fold 1 will be validation data, and the rest will be training. In the 2nd set, fold 2 will be a validation and the rest will be training, so next up to the 7th set. Thus, cross validation can increase the accuracy of predictions at the exact number of multiples [12].

**Model Evaluation**

Target organ evaluation is carried out by comparing the values of the homogeneity index (HI) obtained from predictions and clinics. Mathematically it can be written in equation (5) [17];

$$HI = \frac{(D_2 - D_{98})}{D_{50}} \tag{5}$$

where HI represents the homogeneity of the dose distribution at the target, where the ideal value for HI is close to zero, while the evaluation of each feature is to find the difference between the predicted value and the clinical planning value for the doses mean and max on OAR and  $D_2$ ,  $D_{50}$ , and  $D_{98}$  for PTV, which can be written in equation (6) [18];

$$DD_x = |D_x^{RF} - D_x^{klinik}| \tag{6}$$

where  $DD_x$  is the dose difference between the prediction and the clinical plan,  $D_x^{RF}$  is the dose x of the prediction random-forest, and  $D_x^{klinik}$  is the dose x of the clinical plan.

The evaluation of the model in this study was carried out by determining the value error of the training and testing sets. The value is an error analyzed with the equation Mean Absolute Error (MAE), which can be written mathematically as in equation (7) [19];

$$MAE = \frac{1}{n} \sum_{i=1}^n |y_i - \hat{y}_i| \tag{7}$$

where n represents the amount of data,  $\hat{y}_i$  represents the clinical planning value and  $y_i$  is the prediction value of random-forest.

**Statistical Analysis**

In addition, statistical tests were also carried out using a non-parametric paired t-test, namely the Wilcoxon matched-pairs signed rank test using GraphPad 9.3 to see if there was a significant difference between the two data, with a probability value of  $p \leq 0.05$  indicating a significant difference between the two data and  $p > 0.05$  indicating that there is no significant difference between the two data [20].

**Results**

**Target Prediction**

Targets were predicted for the  $D_2$ ,  $D_{50}$  and  $D_{98}$  features of the PTV organ. Figure 4 shows a box plot of the clinical planning value as the true value represented by the yellow box and the predicted value represented by the green box. It can be seen that the distribution of the data on the actual value is wider than the predicted value. In Table 1, the average difference between the prediction and the actual value can be seen, and the error in the PTV feature is evaluated using  $MAE < 0.02$ . In detail, the value of MAE for PTV features are  $D_2$  (0.012),  $D_{50}$  (0.015) and  $D_{98}$  (0.018).

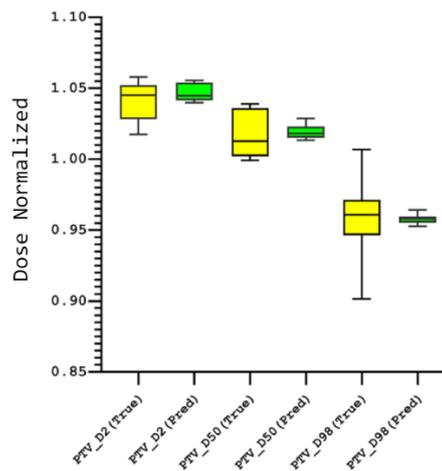


Figure 4. Box plot of clinical value or true value (yellow) vs. predicted value (green) from 18 testing data at the PTV features

**OAR Prediction**

The features evaluated in OAR consist of the right lung (RL), left lung (LL), heart, and spinal cord (SC), with each feature containing the average dose ( $D_{mean}$ ) and maximum dose ( $D_{max}$ ). Figure 5 shows a box plot of the actual value represented by the yellow box and the predicted value represented by the green box. The average difference obtained from the OAR feature can also be seen in Table 1 and the error value obtained by  $MAE < 0.3$ . In detail, the value of MAE for OAR features ( $D_{mean}$  and  $D_{max}$ ) are the right lung (0.104 and 0.228), left lung (0.094 and 0.27), heart (0.088 and 0.267), spinal cord (0.069 and 0.121) and ( $V_{95}$ ) Body (0.094).

Table 1. Summary of mean±standard deviation, absolute difference, MAE, and statistical test of value p- for each prediction

Organ	Feature	Mean ± SD		DDx	MAE*	p-value**
		Clinic	Prediction			
PTV	D2	1.04 ± 0.013	1.05 ± 0.006	0.012±0.010	0.012	0.246
	D50	1.02 ± 0.016	1.02 ± 0.005	0.015±0.007	0.015	0.393
	D98	0.96 ± 0.023	0.96 ± 0.003	0.018±0.017	0.018	0.766
	HI	0.08 ± 0.025	0.087 ± 0.006	0.02±0.016	0.02	0.154
Body	V95	1.17 ± 0.116	1.20 ± 0.117	0.094±0.092	0.094	0.060
Right Lung	Mean	0.19 ± 0.159	0.20 ± 0.047	0.104±0.08	0.104	0.442
	Max	0.75 ± 0.314	0.80 ± 0.111	0.228±0.153	0.228	0.551
Left Lung	Mean	0.21 ± 0.149	0.21 ± 0.101	0.094±0.066	0.094	0.832
	Max	0.77 ± 0.319	0.73 ± 0.126	0.270±0.106	0.270	0.702
Heart	Mean	0.16 ± 0.16	0.15 ± 0.077	0.088±0.104	0.088	0.734
	Max	0.79 ± 0.363	0.71 ± 0.255	0.267±0.238	0.267	0.099
Spinal Cord	Mean	0.15 ± 0.12	0.12 ± 0.047	0.069±0.067	0.069	0.393
	Max	0.51 ± 0.182	0.44 ± 0.107	0.121±0.071	0.121	0.067

\*MAE is Mean Absolute Error  
 \*\*p-value > 0.05 is insignificant difference  
 \*\*p-value < 0.05 is significant difference

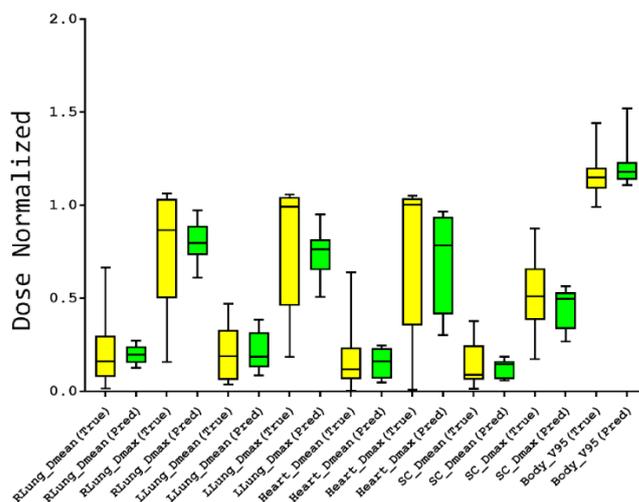


Figure 5. Box plot of clinical value or true value (yellow) vs. predicted value (green) from 18 testing data at the OAR features

### Discussion

This study uses a radiotherapy planning database with IMRT technique to as many as 60 data points for cases of lung cancer patients, where the data is divided into 42 training data and 18 testing data. The researcher developed a machine learning-based dose distribution prediction method with the RF model, where the predicted results will be compared with the clinical planning value as the actual value. Both prediction models will be compared by calculating the difference value, and the RF model will be evaluated using MAE. Next, a statistical test will be carried out to see if there is a significant difference between the two datasets using the Wilcoxon test.

Figure 4 and Figure 5 are box plots for PTV and OAR between the true value (yellow) and the predicted value (green). It can be seen that the data distribution for the predicted value is smaller than the data distribution for the actual value. However, most of the predicted values are still within the range of 25% - 75% of the

actual data (the data depicted in the box is a 25% - 75% data distribution; the line inside the box is the average value, and the line outside the box is the upper value and lower).

From Body V<sub>95</sub> features, calculations were performed manually to obtain the HI values, which obtained a more homogeneous clinical planning with an average HI value of 0.08 ± 0.025 while the HI for prediction was 0.09 ± 0.006.

The value of the difference and error, in this case is MAE, is higher in the OAR feature compared to PTV. This is because the data used still contains OAR features containing PTV volume, which will weaken the model's ability to predict even though the PTV feature error is relatively small. This can be minimized by eliminating PTV volume from the OAR and selecting more specific cases, such as cases of right or left lung cancer only.

In addition to case selection and tumor location, machine learning performance can also be improved by increasing the amount of learning data for machine

learning itself. Because the more data machine learning learns, the more accurate the predictions will be. This is because machine learning will be more familiar with similar data. Because the data used in this study only amounted to 60 data, it is still very small when compared to previous studies that used hundreds of data. Multicenter data retrieval can also be done to enrich the amount of data. However, considering the type of treatment used, such as the modality of the linac aircraft and the treatment planning system method, will avoid data bias that will worsen the prediction results.

Based on the results of statistical test using the Wilcoxon test, by evaluating the probability values presented in Table 1, it can be seen that there is no significant difference in all the predicted features, so this method can predict the dose distribution close to the true value in lung cancer cases with IMRT and can be developed for further research.

Ahn et al., 2021 developed an IMRT planning method (50 data training) based on deep learning (DL) and RapidPlan in breast cancer cases, which were then compared with clinical planning. This research (RF, which is one of the models of ML) consists of 42 training datasets compared to the deep learning method that has been done previously on 2 PTV features, namely  $D_2$  and  $D_{50}$ . The results show a difference of <1%. Furthermore,  $D_2$  for ML and DL is 0.012 and 0.01 (the difference is 0.002 or 0.2%), and  $D_{50}$  is 0.015 and 0.0086 (the difference is 0.0064 or 0.64%). Ahn et al. showed a smaller error value compared to the study, but this was also supported by more learning data. In addition, DL has also implemented deeper learning than ML. More about DL can be found in the paper Ahn et al., 2021.

Based on the results that have been obtained and comparisons with previous studies, prediction performance can be improved by adding training data that will improve model performance and can also use deep learning methods or other methods. The decrease in model performance can also be caused by learning data where the contours of healthy organs still contain PTV volume (OAR+PTV), so that better results can be obtained by removing the PTV volume contour from the OAR (OAR-PTV). Further research can apply to the things mentioned above.

## Conclusion

From the results of this study, it can be concluded that random-forest can predict PTV features well enough so that it can be the basis of the dose distribution prediction algorithm and be developed in future studies. As for the OAR feature, it still has an MAE error value of maximum dose  $> 0.1$ , so it is necessary to increase the case study training datasets that are more specific for the right lung or left lung only and to evaluate other methods of AI.

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