A Unified Framework to Integrate SPECT Perfusion Imaging with Dose-volume Metrics for Estimation of Radiation Pneumonitis

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Research

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A unified framework to integrate SPECT perfusion imaging with dose-volume metrics for estimation of radiation pneumonitis

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Abstract

Background: Single photon emission computed tomography (SPECT) images provides functional information in both diagnosis and radiation therapy. This study aimed to evaluate a unified framework of different approaches and find the optimal one in integrating SPECT lung perfusion imaging into radiotherapy to estimate radiation pneumonitis.

Methods: Twenty-five patients with thoracic tumors were included in this study. All patients had SPECT perfusion imaging before radiotherapeutic treatment. The SPECT images were registered to the planning computed tomography (CT) via a rigid-body transformation. Then a unified framework was presented to integrate functional information with anatomical information to generate functional dose-volume parameters. The framework contained different mapping approaches using uniform, thresholding, linear or non-linear functions. To compare the different approaches in the unified framework, the ability of predicting lung toxicity outcome was evaluated via the receiver operating characteristic (ROC) curve analysis.

Results: Functional dose-volume metrics defined using the linear function achieves the highest value of area under the curve (AUC), compared to those defined with the other three types of mapping functions. With the linear mapping function, significant factors for predicting radiation pneumonia ($p < 0.05$) includes the functional mean lung dose (fMLD) with the threshold of 50-100% and lung volume receiving more than 30 Gy dose (fV_30) with the threshold of 60-100%, among which fMLD showed the highest prediction accuracy (AUC=0.772, threshold=50-100%).

Conclusions: We proposed a framework of functional dose-volume metrics to predict the outcome of radiation pneumonitis. The metrics using the linear function outperform the others.

Keywords: Non-small cell lung cancer, SPECT/CT, Functional dose-volume metrics, radiation pneumonitis

Background

Radiation therapy (RT) is widely used in the treatment of non-small cell lung cancer[1], where dosage is always an important issue. The risk of radiation-induced pulmonary toxicity increases with the dose escalation, limiting the survival greatly[2, 3]. For reasonably formulating radiotherapy plans, researchers have groped for indicators to accurately predict radiation pneumonia (RP), which is one of the most common forms of toxicity.

Popular indicators include the mean lung dose (MLD) and V_i (the volume of lung receiving more than i Gy dose) parameters. Studies have reported that the V_5, V_{20} and MLD were associated with the occurrence of RP[4-7]. However, these metrics assume all lung tissues have equal importance, which is not accurate[8-11]. Increasing evidence shows the higher the lung function, the worse the toxicity after radiotherapy[12, 13]. Then dose-volume metrics with functional information were raised, which used SPECT lung perfusion images to semi-quantitatively analyze the distribution of blood vessels and reflect pulmonary function[14]. Such functional dose metrics were shown the potential to reduce the radiation-induced lung toxicity and improve the prediction of RP risks than anatomical dose metrics [10, 11, 15-19].

There are no unified methods introducing the functional information into radiation therapy. Two main approaches can be summarized according to the existing reports. One defines the functional lung by a threshold. Ding et al.[20] found that 20% of the maximum SPECT count may be the optimal threshold to define the functional lung. The threshold is a tricky parameter ranging from 20% to 90%, of which 70% and 30% are the most common[21]. The other approach utilizes the weighting function based on functional images. Vinogradskiy et al.[13] and Yamamoto et al.[22] weighted each voxel linearly by its CT ventilation value. Some scholars considered any voxels with a SPECT perfusion intensity of 80% or more of the maximum as totally functional[10, 11, 23], and weighted other voxels (below the 80th percentile) linearly according to their SPECT counts. The weighting function can be designed differently.

This study evaluated different weighting functions in a unified framework to encompass functional

information from SPECT lung perfusion imaging. We calculated dose-volume parameters based on different weighting functions and evaluated the ability of predicting the lung toxicity after radiotherapy for non-small cell lung cancer to find the optimal predictor.

Methods

Patients

This study included a total of twenty-five patients (52-77 years) with thoracic tumors treated with radiotherapy at at Renji Hospital affiliated to the School of Medicine in Shanghai Jiao Tong University. No patients had chest radiotherapy before acquiring images and all were treated between 2012 and 2016. Table 1 lists the patient information.

Image acquisition and processing

All patients underwent SPECT perfusion imaging before radiotherapy. The patients were scanned on the Philips Precedence (Philips Healthcare) in the supine body position following an intravenous injection of 4 mCi of technetium-99m (^{99m}Tc) labeled with macroaggregated albumin (^{99m}Tc-MAA). The planning CT data were acquired with a slice thickness of 5 mm using the GE HiSpeed NXi CT simulator (GE Healthcare). Radiotherapy treatment planning was performed by the medical physicist without regard to the functional lung perfusion imaging data. The volume of the lungs described does not include the volume of the gross tumor volume GTV. Using SlicerRT[24], an extension of 3D Slicer for radiation therapy research, we created accumulated dose volumes. The registration was carried out in the Medical Image Processing Analysis and Visualization (MIPAV) software (http://mipav.cit.nih.gov; National Institutes of Health)[25]. Fig. 1 shows one example of the fusion results.

Dose metrics in the unified framework

Fig. 2 illustrates different mapping functions from the physical volume to the function volume of voxel. Fig. 2(a) is

a uniform function. Fig. 2(b) is corresponding to the functional dose-volume metrics with a threshold. In Fig. 2(c), with x% of maximum SPECT count value as the threshold, a linear mapping function W_l is defined. W_l is proportional to the SPECT intensity below the threshold value x%. In this work, we set x% to be 40-100%, and find an optimal one for the best estimation of RP.

In Fig. 2(d), we defined a non-linear function W_{nl}:

$$W_{nl}(\gamma) = (\frac{Q_\gamma}{Q_{max}})^\alpha$$

where Q_γ is the perfusion value in γth voxel and Q_{max} is the maximum perfusion value. The parameter α ranges from 0.25 to 4. When $\alpha = 1$, the mapping function becomes linear and is equivalent to Fig. 2(c) with x%=100%.

Our unified framework includes both standard and functional dose-volume parameter. Standard dose metrics contain the MLD and the percentage of lung volumes receiving more than certain Gy dose (V_5, V_{10}, V_{20} and V_{30}, respectively). Functional dose metrics are similar to the standard ones, only substituting the physical voxel volume with the functional voxel volume[10, 11]. Consequently, we defined the fMLD_x in Gy and functional percentage $\mathrm{f}_x\mathrm{V}_i$ with different mapping (or weighting) functions as follows:

$$\mathrm{fMLD}_x = \sum \frac{D(\gamma) \times W(\gamma)_x}{N}$$

$$\mathrm{f}_x\mathrm{V}_i = \frac{\sum W(\gamma_i)_x}{N}, i = 5, 10, 20, 30$$

where $D(\gamma)$ is the dose in the physical voxel γ (γ_i is the voxel receiving radiation dose more than i Gy), W_x is the mapping function shown in Fig. 2.

Toxicity assessment and statistical analysis

Patients were evaluated during the follow-up visits after completion of RT. Radiation pneumonitis were diagnosed by radiation oncologists and graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03 criteria[26]. In our study, grades 3-5 were considered as the RP group, and grades 1-2 were

non-RP group.

Statistical analysis was carried out utilizing IBM SPSS Statistics software package (version 24, IBM Corp., Armonk, New York, USA). For estimating the ability of each dosimetric parameter in predicting radiation pneumonitis, independent-samples t-test was conducted. The normality of the sample data had been verified by Shapiro-Wilk test.

Results

Seventeen patients (68%) were diagnosed with RP (grade 3-5) during the follow-up visits after completion of RT. Median follow-up period was 12 months (7~18 months).

As shown in Fig. 3, it is evident that all these parameters are higher in RP than in non-RP patients. However, the difference between the RP and non-RP groups varies with mapping functions. The independent-samples t-test show no significant differences between groups when using the dose-volume parameters calculated via threshold or nonlinear mapping functions, while all the fMLD, fV_{20} and fV_{30} for linear mapping function have a significant difference between RP and non-RP groups. Table 2 also lists the mean and standard deviation for each of them.

We plot the AUC values in Fig. 4(a) for all significant dosimetric parameters using different weighting thresholds. It is confirmed that functional information integrated via the linear weighting function improved the accuracy to predict the radiation pneumonitis. Furthermore, linear weighting performs better than threshold weighting. Among all the parameters using the linear weighting function, fMLD outperforms others. For different thresholds larger than 80% in the linear weighting function, AUC values remain invariant. Fig. 4(b) illustrates the highest prediction accuracy is achieved in the parameter fMLD when the threshold for weighting function is 50-100% (AUC=0.772).

When using non-linear weighting function, the highest AUC is found in fMLD with parameter α being 0.71 (AUC=0.721) and the worst AUC is found in V_{10} with parameter α being 0.25 (AUC=0.632). However, none

parameters using non-linear weighing function reach a significant level of 0.05.

Discussion

In this study, functional information of SPECT lung perfusion images was introduced into the RT planning via a unified framework with different mapping functions. We used the framework to incorporate all the popular dose-volume metrics and evaluated their ability of predicting the toxicity of RT for finding the optimal metric.

As shown in Fig. 3 and 4, functional dose-volume parameters usually have better predictive ability than standard dose metrics, which is consistent with other findings [10, 11, 13, 15, 16, 27]. After introducing the functional information, fMLD and fV_20 are the most common factors related to the incidence of RP[10, 11, 13, 28]. According to our study, however, fV_20 could not predict RP. ROC analysis demonstrates that when the linear weighting function is used, fMLD with the threshold of 50-100% and fV_30 with the threshold of 60-100% (interval of 10%) are capable of predicting RP. And fMLD with 50-100% threshold is the best predictor of RP. In addition, non-linear weighting function could not improve the accuracy to predict the outcome of radiation pneumonitis either, compared to the linear weighting function. These were consistent with the results reported in the literature[14, 27, 29].

Our results showed that fMLD performs best to predict radiation pneumonitis in linearly weighting the SPECT lung perfusion imaging with a threshold being 80% or more. However, the definition of toxicity endpoint has been controversial. The more severe RP is, the more relevance on clinic, meanwhile the lower incidence is, which limits the statistical power of analysis based on severe events[30]. Although more scholars have chosen grade 2 or higher RP as the endpoint[10, 11, 29-32], there are still lots of literatures associated with grade≥3 RP[6, 27, 33-35]. Grade 3 or higher RP has more threats to life; hence it is more clinically significant to select grade 3 or higher RP as the endpoint, as we did in this study.

Conclusions

In this study we proposed a unified framework to incorporate the functional information form SPECT perfusion imaging into the dose-volume metrics. This framework includes approaches to the conventional metrics which does not include the functional information, and to the functional metrics with three different types of mapping functions. When weighting the SPECT images linearly, a threshold of 80% of SPECT count value or more were better to predict radiation pneumonitis. Functional MLD with the threshold of 50-100% and fV_{30} with the threshold of 60-100% were significant predictors associated with RP. Compared to linear weighting function, thresholding and non-linear weighting functions could not improve the accuracy to predict the outcome of radiation pneumonitis. Functional dose metrics with appropriate weighting threshold would be conducive to the radiotherapy treatment for patients with non-small-cell lung cancer. It is worth noting that additional exploration is essential to be performed for verification of our results.

Abbreviations

SPECT: Single photon emission computed tomography; CT: computed tomography; ROC: receiver operating characteristic; AUC: area under the curve; fMLD : functional mean lung dose; RT: Radiation therapy; RP: radiation pneumonia.

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Authors' contributions

All authors read and approved the final version of the manuscript. Idea and conception: P.L., X.L., Q.H., and X.M. Data collection: L.D., X.Z. and X.W. Modeling and experiment: P.L., X.L. and L.D. Data interpretation: P.L., X.L. and L.D. Manuscript writing: P.L. and X.L. Manuscript review: P.L., Q.H., and X.M.

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Availability of data and materials

The data and materials of this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee of Ruijin Hospital of Chnia with the exemption for patient consent. The purpose, scope, benefits, risks, and procedures of the study were explained to each volunteer.

Consent for publication

The author grants the publisher the sole and exclusive license of the full copyright. The authors guarantee that this manuscript has not been previously published elsewhere. The authors declare that any person named as co-author of the contribution is aware of the fact and has agreed to being so name.

Competing interests

The authors do not have any conflict of interest to declare.

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Figure Legends

Fig. 1. An example of fusion of structural and functional information after registration. The planning CT with raw functional SPECT image (left) and the planning CT with SPECT-weighted image with a threshold of 80% of maximum SPECT count value (right).

Fig. 2. A unified framework of integration of functional information via different mapping functions:(a) standard, (b) thresholding, (c) linear and (d) non-linear. The functions map from the physical volume of voxel to the function volume of voxel.

Fig. 3. The mean lung dose (MLD) and V_i corresponding to different mapping functions defined in Fig. 2. Each subfigure showed the mean and standard deviation for both the RP group and the non-RP group in three sections: thresholding (left), linear (middle) and non-linear (right). Significant parameters are indicated by an asterisk.

Fig. 4. The ability of predicting RP. (a) AUC values for dosimetric parameters using linear mapping functions (solid lines) and threshold mapping functions (dash lines) to predict RP. The right most dot on each dash line is corresponding to the standard dose metric. (b) ROC curves with AUC values for dosimetric parameters that reached a significant level of 0.05. They are all defined using the linear mapping functions. The black dot represents RP, the red square represents non_RP.

Table 1. Patient characteristics (*N*=25).

Characteristics	***N* (%)**
Age (y)	
Range	52-77
Median	62
Sex	
Male	23 (92)
Female	2 (8)
Dose description (Gy)	
Range	46-76
Median	60
RP	
Grade 1-2	8 (32)
Grade 3-5	17 (68)

Table 2. Independent-samples t-test of dosimetric parameters in patients with RP and without RP.

Parameters	**non-RP group (mean ± SD)**	**RP group (mean±SD)**	***p* value**
$\mathbf{fMLD_{40\%}(Gy)}$	11.76±4.51	16.07±4.16	0.028
$\mathbf{f_{40\%}V_{20}(\%)}$	19.72±9.52	26.64±6.83	0.049
$\mathbf{f_{40\%}V_{30}(\%)}$	11.72±7.10	17.65±5.58	0.033
$\mathbf{fMLD_{50\%}(Gy)}$	11.89±4.69	16.44±4.24	0.024
$\mathbf{f_{50\%}V_{20}(\%)}$	19.77±9.58	26.77±6.80	0.046
$\mathbf{f_{50\%}V_{30}(\%)}$	11.53±7.15	17.72±5.59	0.027
$\mathbf{fMLD_{60\%}(Gy)}$	11.99±4.77	16.70±4.27	0.021
$\mathbf{f_{60\%}V_{20}(\%)}$	19.67±9.39	26.87±6.79	0.039
$\mathbf{f_{60\%}V_{30}(\%)}$	11.38±7.04	17.84±5.60	0.021
$\mathbf{fMLD_{70\%}(Gy)}$	12.10±4.77	16.86±4.32	0.02
$\mathbf{f_{70\%}V_{20}(\%)}$	19.65±9.22	26.95±6.83	0.036
$\mathbf{f_{70\%}V_{30}(\%)}$	11.51±6.74	17.93±5.65	0.02
$\mathbf{fMLD_{80\%}(Gy)}$	12.18±4.77	16.93±4.35	0.021
$\mathbf{f_{80\%}V_{20}(\%)}$	19.68±9.15	26.97±6.80	0.035

$\mathbf{f_{80\%}V_{30}(\%)}$	11.65±6.58	17.97±5.69	0.021
$\mathbf{fMLD_{90\%}(Gy)}$	12.20±4.76	16.95±4.37	0.022
$\mathbf{f_{90\%}V_{20}(\%)}$	19.71±9.12	26.96±6.80	0.036
$\mathbf{f_{90\%}V_{30}(\%)}$	11.68±6.52	17.97±5.70	0.022
$\mathbf{fMLD_{100\%}(Gy)}$	12.20±4.76	16.95±4.36	0.022
$\mathbf{f_{100\%}V_{20}(\%)}$	19.71±9.12	26.96±6.80	0.036
$\mathbf{f_{100\%}V_{30}(\%)}$	11.68±6.52	17.98±5.70	0.022

Figures

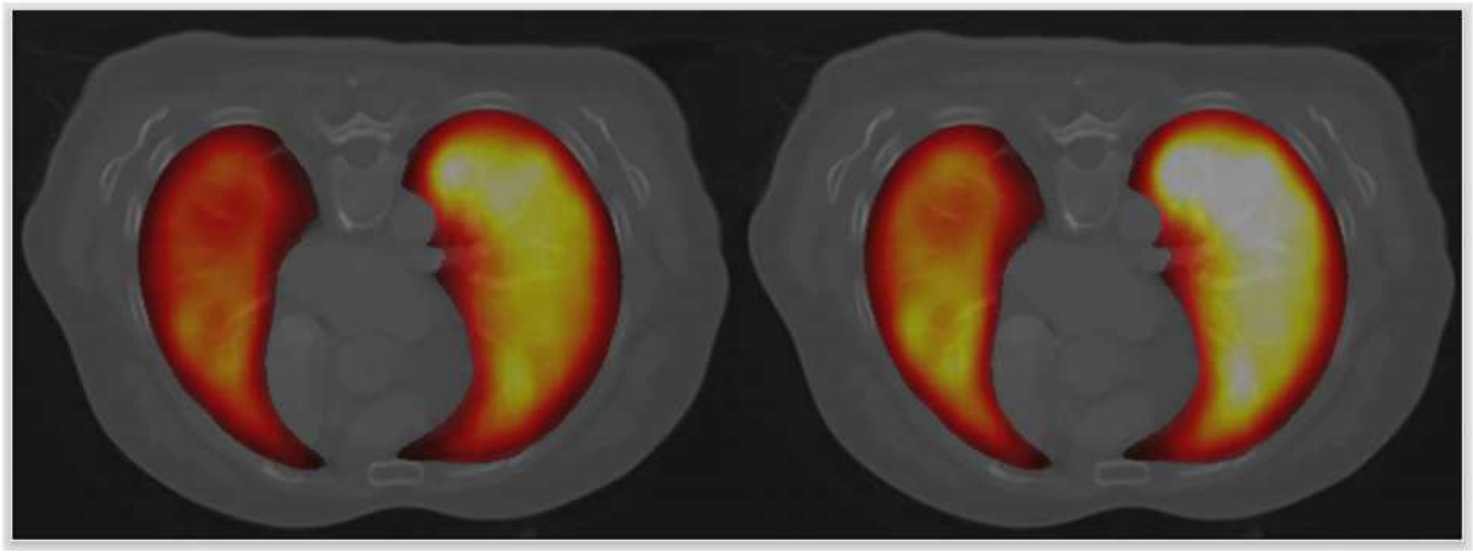

Figure 1

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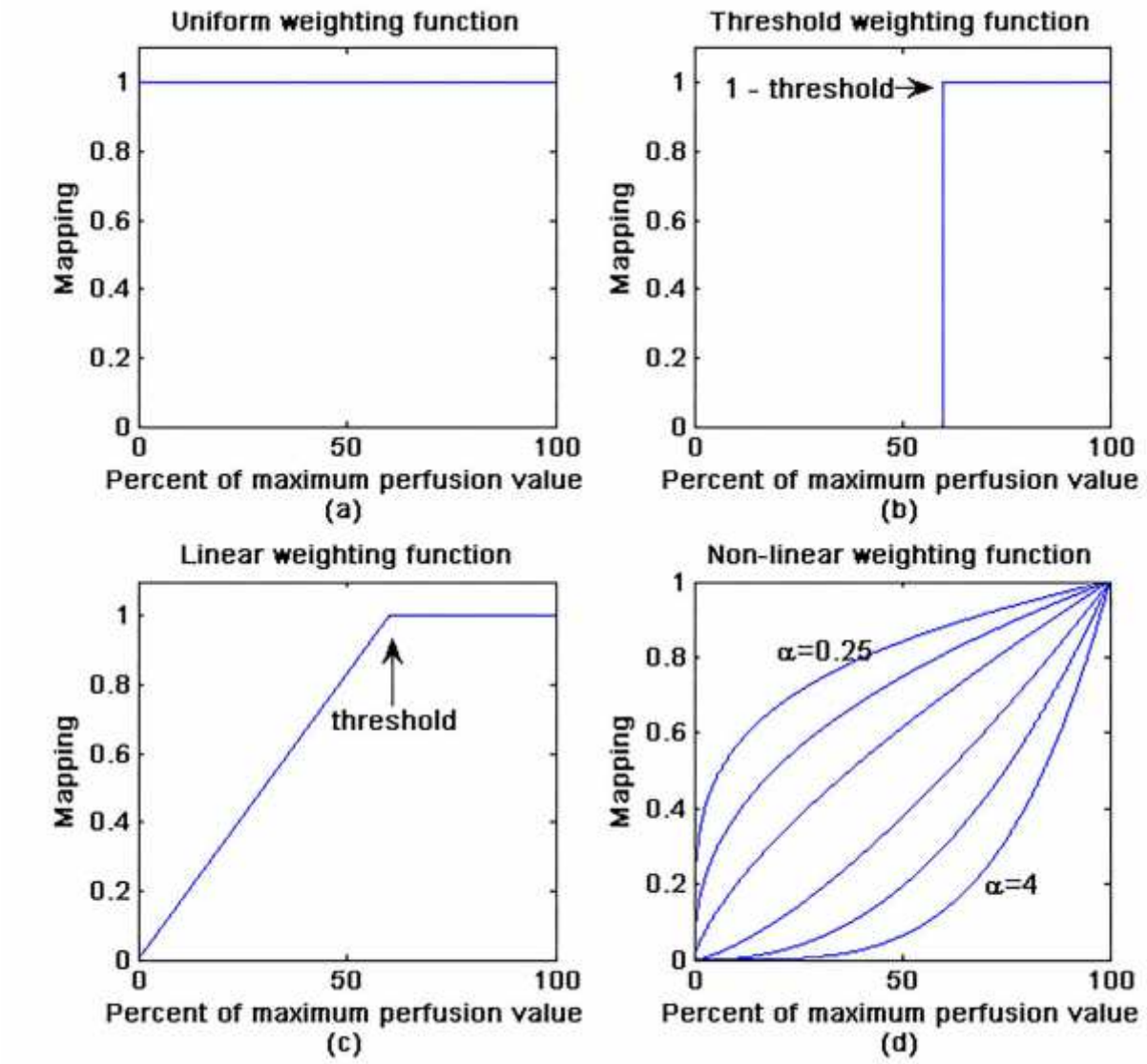

Figure 2

A unified framework of integration of functional information via different mapping functions:(a) standard, (b) thresholding, (c) linear and (d) non-linear. The functions map from the physical volume of voxel to the function volume of voxel.

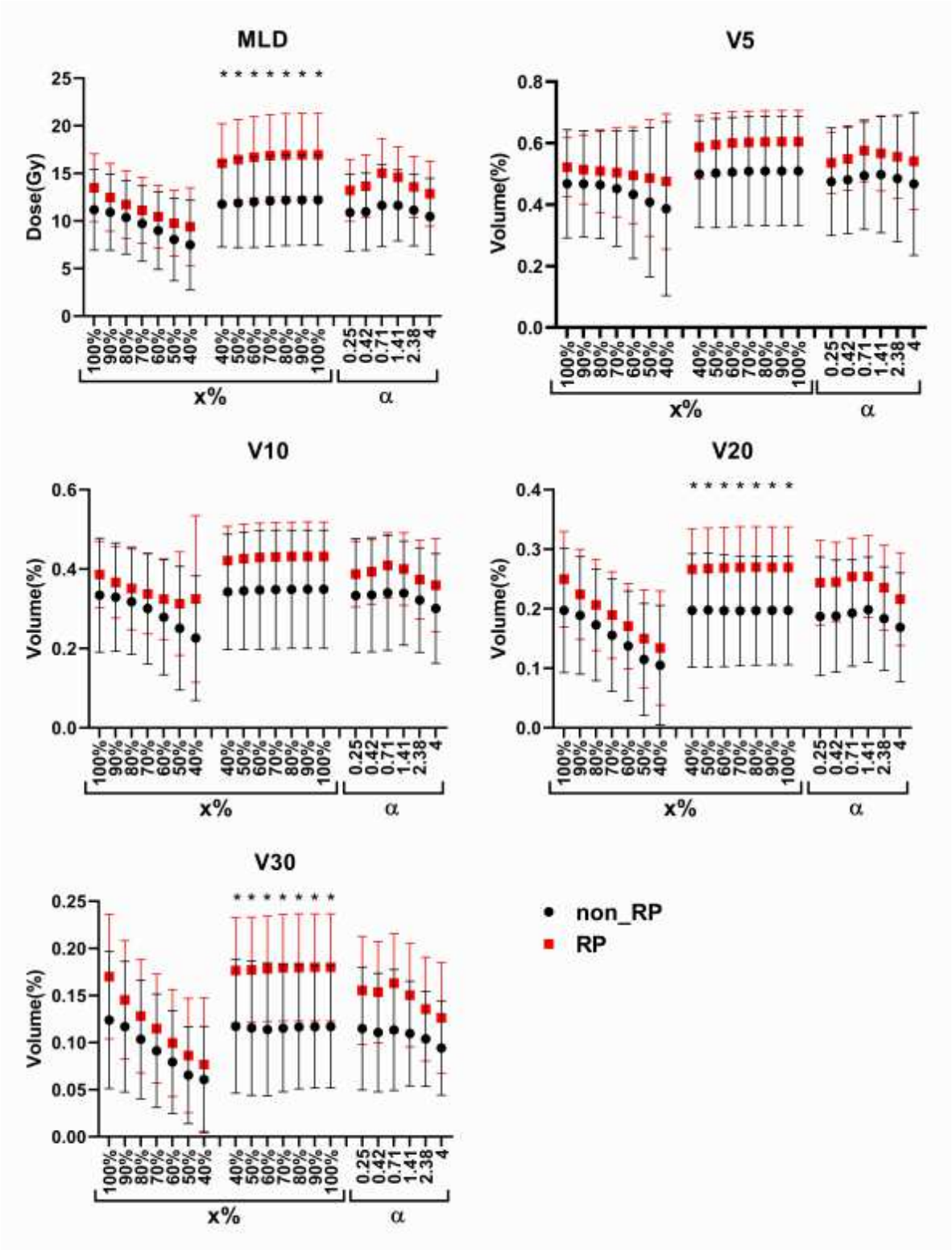

Figure 3

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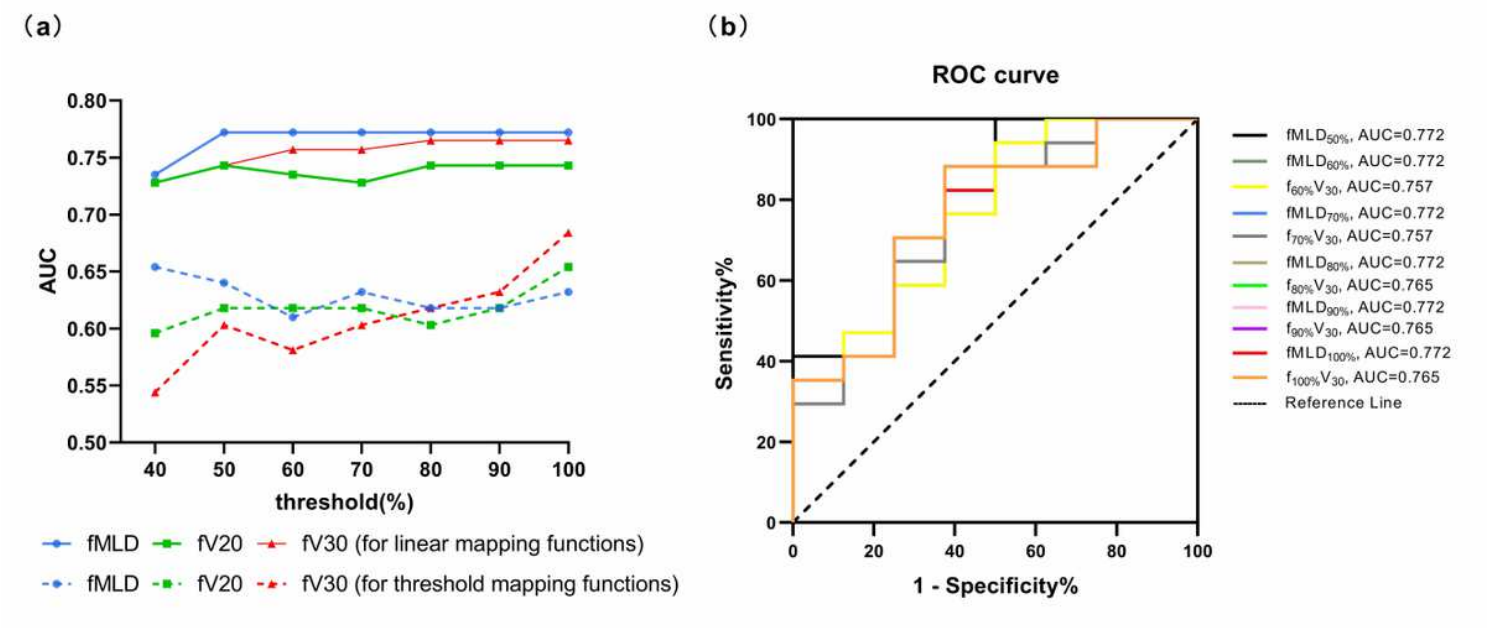

Figure 4

The ability of predicting RP. (a) AUC values for dosimetric parameters using linear mapping functions (solid lines) and threshold mapping functions (dash lines) to predict RP. The right most dot on each dash line is corresponding to the standard dose metric. (b) ROC curves with AUC values for dosimetric parameters that reached a significant level of 0.05. They are all defined using the linear mapping functions. The black dot represents RP, the red square represents non_RP.