Volume 22, No 1 | International Journal of Radiation Research, January 2024

Evaluation of statistical prediction model fitting by combining fiducial markers and lung volume for stereotactic body radiotherapy

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► ***Original article***

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Received: February 2023
Final revised: June 2023
Accepted: June 2023

Int. J. Radiat. Res., January 2024; 22(1): 17-22

DOI: 10.52547/ijrr.21.1.3

Keywords: *Pelvis, Stereotactic body radiotherapy, Four-dimensional computed tomography, Respiratory movement, Statistical prediction model, lung cancer.*

ABSTRACT

Background*:** This study evaluates the tracking accuracy of the lung tumor volume and fiducial markers using four-dimensional computed tomography (4DCT) and fitted neural network models. ***Materials and Methods: This study utilized data from 31 patients (109 fiducial markers) who underwent stereotactic body radiotherapy (SBRT). The respiratory movements of fiducial markers, lung tumors, and lung volume were calculated using 4DCT. Cross-correlation coefficients were then calculated to analyze the phase movements of fiducial markers, lung tumors, lung volume, direction displacement, and lung area (upper, middle, and lower lobes). Statistical prediction models were used to evaluate the predictive accuracy of the left–right (LR), anterior–posterior (AP), cranial–caudal (CC), and three-dimensional (3D) cross-correlation coefficients between fiducial markers and lung tumors. The coefficient of determination (R^2) was used to determine the accuracy of the statistical prediction models for the explanatory variables. ***Results:*** The correlation between fiducial marker and lung tumor, as well as lung tumor movement by time phase, yielded the following R^2 values—LR: 0.920, AP: 0.319, CC: 0.675, and 3D: 0.449 for the upper lobe; LR: 0.567, AP: 0.627, CC: 0.955, and 3D: 0.939 for the middle/lower lobes. Statistically significant differences were observed in the CC and 3D directions within each lower lobe. ***Conclusions:*** The respiratory movements of fiducial markers and lung tumors in lung SBRT show stronger correlation with the movement of lung volume in the middle/lower lobes compared to that in the upper lobes. Combining a fiducial marker with lung volume improves the prediction accuracy of the respiratory movement of lung tumors.

INTRODUCTION

Lung stereotactic body radiotherapy (SBRT) is an advanced treatment approach that effectively manages early-stage primary and metastatic lung cancer. It delivers higher doses of radiation in fewer sessions, improving treatment outcomes [1]. To minimize normal tissue toxicity, this approach commonly uses small treatment fields. However, accurate delivery of a high dose requires careful evaluation of the spatial relationship between the target area and surrounding normal tissues [1].

During radiotherapy, the motion of lung tumors and organs at risk, as well as respiratory and peristaltic activity and cardiac functions, can introduce geometric uncertainties [2, 3]. In this regard, four-dimensional computed tomography (4DCT) is often utilized to assess tumor motion and simulate respiratory and intrapulmonary motion before SBRT [4, 5].

SBRT incorporates a tracking system with fiducial markers as small markers placed in the body to guide and track treatment accuracy, which helps reduce the margins of geometric uncertainties of respiratory motion [6, 7]. The fundamental assumption of tracking techniques is the presence of a strong correlation between fiducial markers and lung tumors [8]. However, the movement of lung volume and the fiducial marker is not perfectly correlated because of the difference in movement depending on the placement position [1, 9]. 4DCT evaluates the respiratory motion correlation between lung tumors and fiducial markers, which allows the margin setting and dose accuracy to be improved for individual patients.

SBRT relies on spirometry and employs a gating method to analyze the quantitative respiratory volume [10, 11]. Furthermore, SBRT uses a combination

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[DOI: 10.61186/ijrr.22.1.17]

of spirometry and fiducial markers to improve the treatment accuracy. 4DCT enables the calculation of three-dimensional (3D) directional respiratory movement features of the lung volume and fiducial marker [12]. In a previous study, we demonstrated the effectiveness of combining lung volume and fiducial markers by analyzing the 3D distance of respiratory movement using 4DCT [12]. However, we did not evaluate the relationship of respiratory movement between lung volume and each direction for different lung regions.

The advantages and disadvantages of a dual-gated system can be analyzed with a neural network model fitting of machine learning (ML) [13, 15]. We believe that constructing a predictive model of the respiratory movements of the fiducial markers and lung tumors simulates the effect of multiple explanatory variables (information on tumor or marker movement and lung volume). To the best of our knowledge, no studies have leveraged the model fitting accuracy of ML to evaluate the relationship of 3D directional respiratory movement between lung volume and fiducial markers.

The present study introduces several novel aspects in the field of lung SBRT. Firstly, it evaluates the tracking accuracy of lung tumor volume and fiducial markers by employing a combination of 4DCT and fitted neural network models. This approach aims to improve the precision and effectiveness in delivering high doses while minimizing damage to surrounding healthy tissue. Secondly, the study investigates the correlation between respiratory movements of fiducial markers, lung tumors, and lung volume, using 4DCT to enhance margin setting and dose accuracy tailored to individual patients. Thirdly, the analysis incorporates 4DCT to calculate 3D directional respiratory movement features of the lung volume and fiducial markers.

By employing machine learning techniques, the study further explores the advantages and disadvantages of a dual-gated system, contributing to a deeper understanding of the relationship between respiratory movement, lung volume, and fiducial markers. Collectively, these novel findings offer valuable insights into safer and more accurate radiotherapy strategies for lung cancer treatment.

MATERIALS AND METHODS

This study used the data of 31 patients (mean age: 79.6 (50–90) years) who underwent pulmonary stereotactic radiotherapy with fiducial markers (a total of 109 markers) implanted between 2018 and 2021. Ethical guidelines outline in the Declaration of Helsinki were followed, and the study received approval from the Institutional Review Board (Yamaguchi University Hospital: H2021-055, Date of registration: 05/16/2022). All cases involving fiducial markers in this study exhibited a respiratory movement of 1 cm or more, as determined through a prior assessment of lung tumor movement using 4DCT. 4DCT images were acquired using a CT scanner (Definition AS Open, Siemens AG, Munich, Germany) equipped with an external real-time position management system (Varian Medical Systems, Palo Alto, CA, USA) and an infrared camera system (Varian Medical Systems, Palo Alto, CA, USA). The 4DCT data were divided into ten phase bins (1% –90%) representing one breathing cycle. Table 1 presents the patient characteristics, including respiratory movement of lung volume, lung tumor, and fiducial markers.

Table 1. Patients' clinical characterization.

Tumor Lung region	Number (patients)	Mean lungs volume(min–max) (ml)	3D distance mean respiratory movement (max)(mm)	
			Tumor	Marker
Right upper lobe	6	2461.7	0.1	1.0
		(1692.0–5190.4)	(13.1)	(16.3)
left upper lobe	10	3286.3	1.0	1.9
		(2159.3–6464.2)	(15.2)	(18.2)
Right middle/ lower lobe	12	2771.4	3.1	3.2
		(1524.0–5337.9)	(26.2)	(55.6)
Left lower lobe	3	2656.2	5.9	5.9
		(2273.1–3723.8)	(19.5)	(20.9)
Total	31	2997.6	1.3	2.1
		(1524.0–6464.2)	(26.2)	(55.6)

Contouring of fiducial markers, lung tumors, and lung volumes using propagation technique

Radiation therapy planning support software (MIM Software Inc., OH, USA) was used to propagate the lung tumor to all phase images of 4DCT. The initial contouring of the lung tumor was performed by an oncologist using CT [16]. Additionally, the fiducial markers and lungs were propagated from the contoured 50% respiratory phase 4DCT to all other phase 4DCT images. The fiducial markers, lung tumor, and lung volumes were visually confirmed and corrected by the radiologist. Lung volumes for all patients were calculated using the entire set of phase 4DCT images.

Evaluation of respiratory movement of fiducial markers and lung tumor in 4DCT images

First, the positional coordinates --of fiducial markers and the lung tumor were calculated for each phase using radiation therapy planning support software. Second, the cross-correlation coefficients (CCC) of left–right (LR), anterior–posterior (AP), cranial–caudal (CC), and 3D directions between the fiducial marker and lung tumor were calculated using Equation (1) [17]:

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$$Cross\ correlation\ coefficient = \frac{\Sigma(x-\bar{x})\Sigma(y-\bar{y})}{\sqrt{\Sigma(x-\bar{x})^2\Sigma(y-\bar{y})^2}} \quad (1)$$

where x denotes respiratory movement and y denotes the time phase.

The CCC for LR, AP, CC, and 3D between each direction of the fiducial marker in each phase and the change in the lung volume were also calculated using equation (1).

Furthermore, a statistically significant difference test was performed to compare the CCC between lung volume and the fiducial marker for the upper and middle/lower lobe groups, respectively, to evaluate the variation in respiratory movement in different lung regions.

Model fitting of the CCC for 3D displacement of fiducial markers and lung tumor

An artificial neural network (ANN) was designed and the JMP software (SAS, Cary, NC, USA) was used for determining the following parameters: explanatory variables for each direction (LR, AP, CC, and 3D), distance between the fiducial marker and lung tumor (A group), CCC for each direction displacement (LR, AP, and CC) of markers and the lung tumor, and each direction displacement (LR, AP, CC, and 3D) of the lung volume and lung tumor (B group) and of all groups (A and B groups) [18,19]. The explanatory variables for groups A and B were additionally calculated and divided into two groups (upper and middle/lower lobes). The penalized maximum of single-layer ANNs with Tanh functions was used in the model fitting, and the reproducibility of the model was evaluated by constructing it for 30 iterations using a random sampling method. The effect of direction displacement was assessed using the coefficient of determination R^2 and JMP software was employed for sensitivity analysis in model fitting.

Statistical analysis

Statistical significance was used the Mann-Whitney U test (statistically significant when p values < 0.05) using JMP Pro 15 statistical software.

RESULTS

Table 1 lists the range of respiratory movement for the positional coordinates of the fiducial marker (mean: 2.1 mm; max: 55.6 mm) and lung tumor (mean: 1.3 mm; 26.2 mm), as well as the lung volume (mean: 2997.6 ml; range: 1524.0–6464.2).

Figure 1 presents the CCC for the respiratory movements between the fiducial markers and lung tumor, as well as that between the lung volumes and fiducial markers. The CCC of three directions (LR, AP, and 3D) between fiducial markers and the lung tumor show a higher correlation compared to those between the lung volume and fiducial markers. The CCC between the lung volume and lung tumor are significantly different, except for the CC direction. Figure 1 also demonstrates a statistically significant difference in CCC between the A and B groups.

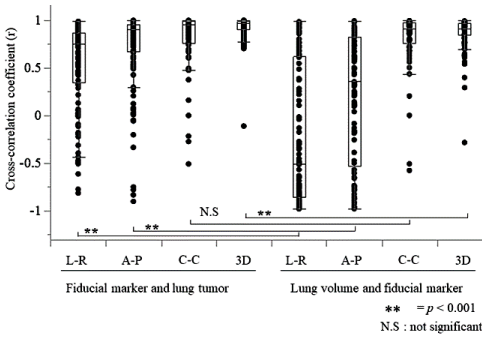


Figure 1. Cross-correlation coefficients of A and B groups. LR: left–right, AP: anterior–posterior, CC: cranial–caudal, and 3D: three-dimensional.

The results for CCC between the fiducial marker and lung volume in the upper and middle/lower lobes are presented in figure 2 and table 2. The R^2 values corresponding to the mean CCC between fiducial markers and lung volumes were negative (LR and AP directions: −0.155 and −0.307; LR direction in the middle /lower lobes: −0.307).

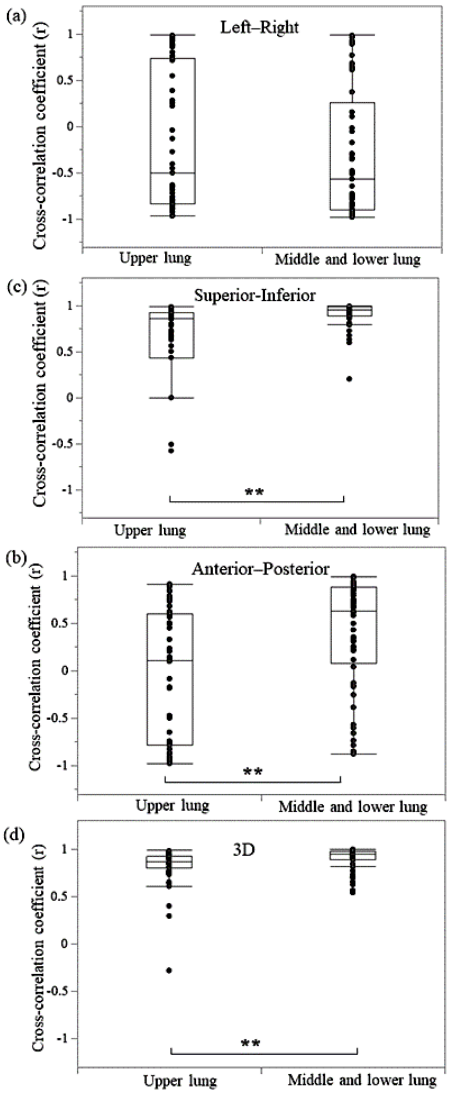


Figure 2. Cross-correlation coefficients of the respiratory movements of lung volume and fiducial markers for the upper and middle / lower lobes groups. **(a)** left-right, **(b)** anterior-posterior, **(c)** cranial-caudal, and **(d)** three-dimensional LR: left-right, AP: anterior-posterior, CC: cranial-caudal, 3D: three-dimensional.

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Table 2. Relationship between fiducial markers and respiratory changes in lung volume.

Area	Direction	Mean CCC between lung volumes and fiducial markers	Standard deviation of lung volumes and fiducial markers	95% confidence level (lower)	95% confidence level (upper)
Upper lobes	LR	−0.155	0.742	−0.364	0.054
	AP	−0.0491	0.702	−0.246	0.148
	CC	0.616	0.426	0.497	0.736
	3D	0.820	0.206	0.762	0.878
Middle / lower lobes	LR	−0.307	0.691	−0.490	−0.123
	AP	0.389	0.583	0.234	0.543
	CC	0.909	0.131	0.874	0.943
	3D	0.901	0.112	0.871	0.931

The CCC values for AP, CC, and 3D directions between the lung volume and fiducial markers differ significantly. The mean CCC and lower/upper 95% confidence levels are higher in the middle/lower lobes compared to the upper lobe. Statistically significant differences are observed in the 3D displacements, and the mean, lower, and upper 95% confidence levels of the CCC are relatively higher in the middle /lower lobes. The sensitivity analysis results for model fitting with the displacement of fiducial markers and the lung tumor for three types of explanatory variables and two groups (upper and middle/lower lobes) are shown in figure 3.

Notably, the R^2 value is low (mean coefficient of determination R^2: 0.109) for the distance between the fiducial markers and lung tumor. Furthermore, the sensitivity of model fitting is not significantly different between the lung tumor and fiducial marker (mean R^2: 0.398) or between the fiducial marker and lung volume (mean R^2: 0.530). However, R^2 values for all explanatory variables are higher (R^2: 0.720) than those for the other variables and the difference is statistically significant, as shown in figure 3. There is no statistically significant difference in R^2 values between the upper and middle/lower lobes, but the result for the middle/lower lobes (R^2: 0.782) is higher than that for the upper lobe (R^2: 0.637).

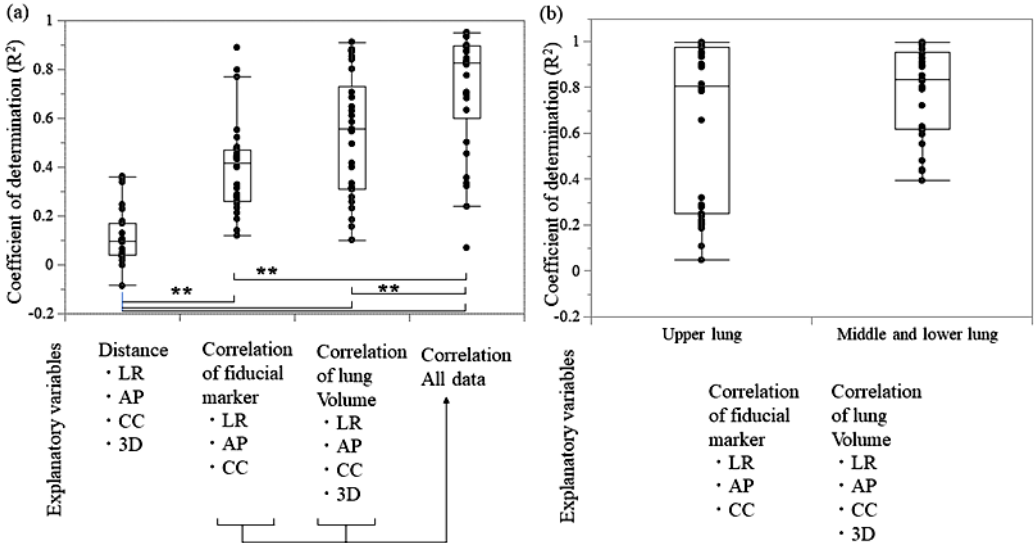


Figure 3. Sensitivity analysis for model fitting of displacement of fiducial markers and lung tumor for three types of the explanatory variables. **(a)** Complete data and **(b)** upper and middle/lower lobes groups LR: left–right, AP: anterior–posterior, CC: cranial–caudal, and 3D: three-dimensional.

DISCUSSION

The CCC of respiratory movements between fiducial markers and the lung tumor showed high values in the LR, AP, and 3D directions compared to those in lung volumes and fiducial markers. This indicates accurate tracking of fiducial markers near lung tumors compared to the significant averaging movement of lung volume [20]. However, the respiratory movement of the fiducial marker and lung tumor is not perfect, and the difference in position may have influenced the trajectory of the fiducial marker. The CC direction did not show a statistically significant difference between the fiducial marker and lung volume, suggesting that lung volumes can improve tracking accuracy by providing averaged stable information [1, 12, 21].

The CCC of respiratory movements between lung volume and the fiducial marker in the upper and middle/lower lobes were statistically significant in the AP, CC, and 3D directions, with consistently higher values observed in the middle/lower lobes in all cases. In the upper lobe, the mean CCC between fiducial markers and lung volumes showed a negative correlation coefficient in the LR and AP directions. This could be attributed to the complex forces exerted

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[DOI: 10.61186/ijrr.22.1.17]

by the contraction of the diaphragm and intercostal muscles in the upper lobe, compared to those in the middle/lower lobes [21]. Consequently, the tracking accuracy of lung volume was found to be inferior in the upper lobe when compared to that in the middle/lower lobes.

The sensitivity analysis using model fitting for the 3D displacement of fiducial markers and lung tumor revealed a low coefficient of determination for respiratory movement in each direction. This result is essential for evaluating optimal fiducial markers with high correlation [16].

The model fitting of the explanatory variable between the lung volume and lung tumor based on the fiducial marker did not yield a significant difference. However, when the lung volume and lung tumor were combined, the model fitting improved. The combined dual-gated method may provide a higher accuracy by leveraging the characteristics of the lung tumor and fiducial marker for stable tracking of the lung volume and noise [20].

One limitation of this study is that the fiducial marker was unable to eliminate the uncertainty of movement due to variations in lung tumor volume. Consequently, the exact gating accuracy could not be evaluated. It is believed that statistical reliability would increase with the use of multiple fiducial markers.

In our previous study, we were unable to evaluate the relationship of respiratory movement between lung volume, lung tumor, and fiducial markers in each direction [12]. However, in this study, we were able to evaluate this relationship in each direction using ML model fitting. This evaluation method can be employed to make adjustments before treatment, such as by determining the gantry for fluoroscopy image guidance and the gating window for real-time tumor-tracking SBRT. The method is expected to contribute to improving the accuracy of patient-specific treatment [8, 16]. Furthermore, the data from this study will be valuable for developing safer and novel dual-gating methods utilizing fiducial markers and lung volume in the future.

CONCLUSION

This study evaluated the tracking accuracy of fiducial markers and lung volume tumors using 4DCT and fitted neural network models. The fiducial marker was highly correlated with the respiratory movement of lung tumors in the LR and AP directions. Moreover, the lung volume was highly correlated in the CC direction, which was more effective in the lower lung. Notably, the ML model fitting obtained by combining fiducial markers and lung volume for lung SBRT was more effective compared to solely using fiducial markers.

ACKNOWLEDGEMENT

None.

***Funding*:** The authors did not receive support from any organization for the submitted work.

***Competing interests*:** The authors have no relevant financial or non-financial interests to disclose.

***Availability of data and material*:** Not applicable

***Ethics approval*:** The study was approved by the Ethics Committee of the Institutional Review Board of Yamaguchi University Hospital and conformed to the ethical guidelines of the Declaration of Helsinki (H2021-055).

***Consent to participate*:** The IRB waived the need to obtain patient consent, owing to the retrospective nature of the study.

***Author contributions*:** Y.T., T.D., and M.K. conceptualized the study; Y.T., S.T., and N.H. implemented the methodology; Y.T. conducted the investigation and formal analysis; Y.T. prepared the original draft; Y.T. reviewed and edited the paper; all authors reviewed the manuscript.

Conflicts of interest: *None declared.*

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