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Patient-specific respiratory motion management using lung tumors vs fiducial markers for real-time tumor-tracking stereotactic body radiotherapy

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ABSTRACT

Background and purpose: In real-time lung tumor-tracking stereotactic body radiotherapy (SBRT), tracking accuracy is related to radiotherapy efficacy. This study aimed to evaluate the respiratory movement relationship between a lung tumor and a fiducial marker position in each direction using four-dimensional (4D) computed tomography (CT) images.

Materials and methods: A series of 31 patients with a fiducial marker for lung SBRT was retrospectively analyzed using 4DCT. In the upper (UG) and middle and lower lobe groups (MLG), the cross-correlation coefficients of respiratory movement between the lung tumor and fiducial marker position in four directions (anterior–posterior, left–right, superior–inferior [SI], and three-dimensional [3D]) were calculated for each gating window (≤ 1, ≤ 2, and ≤ 3 mm). Subsequently, the proportions of phase numbers in unplanned irradiation (with lung tumors outside the gating window and fiducial markers inside the gating window) were calculated for each gating window.

Results: In the SI and 3D directions, the cross-correlation coefficients were significantly different between UG (mean r = 0.59, 0.63, respectively) and MLG (mean r = 0.95, 0.97, respectively). In both the groups, the proportions of phase numbers in unplanned irradiation were 11 %, 28 %, and 63 % for the ≤ 1-, ≤ 2-, and ≤ 3-mm gating windows, respectively.

Conclusions: Compared with MLG, fiducial markers for UG have low cross-correlation coefficients between the lung tumor and the fiducial marker position. Using 4DCT to assess the risk of unplanned irradiation in a gating window setting and selecting a high cross-correlation coefficient fiducial marker in advance are important for accurate treatment using lung SBRT.

1. Introduction

Lung stereotactic body radiotherapy (SBRT) with implantation of fiducial markers can help reduce the planning target volume (PTV) margin and dose to organs at risk, such as the lungs and the heart. Real-time tumor tracking with fiducial markers can be performed during lung SBRT despite lung tumor movement caused by respiration if markers within a gating window are tracked [1–3]. The correlation between a fiducial marker and lung tumor movement is the premise underlying lung SBRT [3]; however, tracking fiducial markers having a low correlation with the tumor carries a risk of misdirected irradiation [4].

The respiratory movement of a lung tumor varies greatly depending on the region where it occurs, ranging from a few millimeters to 2 cm in the upper and lower lungs, diaphragm, and near the heart [5,6]. The movement of a lung tumor varies from linear to loop and hysteresis curves, among other movements [5]. Four-dimensional (4D) computed tomography (CT) (4DCT) imaging is useful for understanding the complex respiratory movements of lung tumors and fiducial markers as well as the correlation between the movements of these tumors and markers [7,8].

Radiotherapy planning devices and support software are widely used to evaluate the respiratory movement of lung tumors and fiducial markers. Radiotherapy planning support software enables automatic contouring of lung tumors and fiducial markers and automatic phase-to-

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phase rendering of 4DCT images via nonrigid registration while efficiently evaluating the three-dimensional (3D) distance between a lung tumor and fiducial markers [9,10].

A previous study has reported on the effect of the dose on the distance of the spatial coordinates between a fiducial marker and a lung tumor in CT images of spontaneous expiratory arrest taken as a part of treatment planning and in matched images at the time of treatment [11]. In our previous study, we evaluated the respiratory movement relationship among lung tumor, lung volume, and fiducial markers and showed that the distance between lung tumor and fiducial marker was not correlated in respiratory movement [12]. However, it was not possible to evaluate the respiratory movement relationship between lung tumor and fiducial markers as well as the distance between lung tumor and fiducial markers in each direction focusing on fiducial markers alone [12]. To date, no study has investigated the relationship between the 3D distance between a lung tumor and a fiducial marker and the interphase shift caused by respiratory movement at the time of dynamic tracking during lung SBRT to evaluate the effect of the fiducial marker on the gating window. Therefore, this study aimed to evaluate the relationship between the lung tumor–fiducial marker respiratory movement and the gating window setting using 4DCT.

2. Materials and methods

2.1. Patients and materials

This study involved 31 patients (mean age [range], 79.6 [52–92] years) who had undergone lung SBRT with fiducial markers (1–5) implanted near the lung tumor between 2018 and 2021. A total of 107 fiducial markers were analyzed. Four fiducial markers that were > 5 cm from the center of gravity coordinate of the lung tumors were excluded as they were difficult to track using a real-time tumor-tracking radiotherapy system (SyncTrax, Shimadzu, Kyoto, Japan). The gating window of the real-time tumor-tracking radiotherapy system can be set at $\leq$ 4 mm in case of an actual irradiation.

This 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 (IRB 2019–031-[1]). Furthermore, in accordance with the abovementioned guidelines, the need for informed consent was waived owing to the retrospective nature of the study.

A CT system (SOMATOM Definition AS Open, Siemens AG, Munich, Germany) was used to obtain 4DCT images for treatment planning via a radiation treatment planning system (RTPS, Eclipse ver. 15.1, Varian Medical Systems, Palo Alto, CA, USA). The obtained 4DCT images were divided into 10 bins (phases) of 0 %–90 % of 1 breathing cycle, with 50 % at the maximal expiratory position and both 0 % and 90 % at the maximal inspiratory positions.

The fiducial marker that was implanted near the tumor was monitored using a real-time tumor-tracking radiotherapy system under fluoroscopic guidance. When the fiducial marker is within the gating window, this system irradiates regardless of whether the lung tumor moves during respiration or not. Therefore, the coordinates of the distance of the center of gravity between the lung tumor and fiducial marker must match within the gating window (Fig. 1a). In this study, the fiducial marker was within the gating window but the lung tumor was outside and therefore was not sufficiently irradiated, a situation defined as unplanned irradiation, which is directed toward organs at risk (Fig. 1b). In addition, lung tumors within the gating window were not irradiated because the fiducial marker was outside the gating window, a situation defined as extended irradiation time, which accounts for the time loss (Fig. 1c).

2.2. Drawing lung tumors and fiducial markers in 4DCT images using the automatic contouring method and calculation of spatial coordinates

Using the radiotherapy planning support software (MIM Maestro, MIM Software, OH, USA), the lung tumor contoured by the oncologist based on the CT images at 50 % phase was automatically propagated in a deformed manner at another phase. Subsequently, the fiducial markers on the 4DCT images were autocontoured as structures with > 2000 HU inside the body using MIM Maestro. The propagated lung tumor and
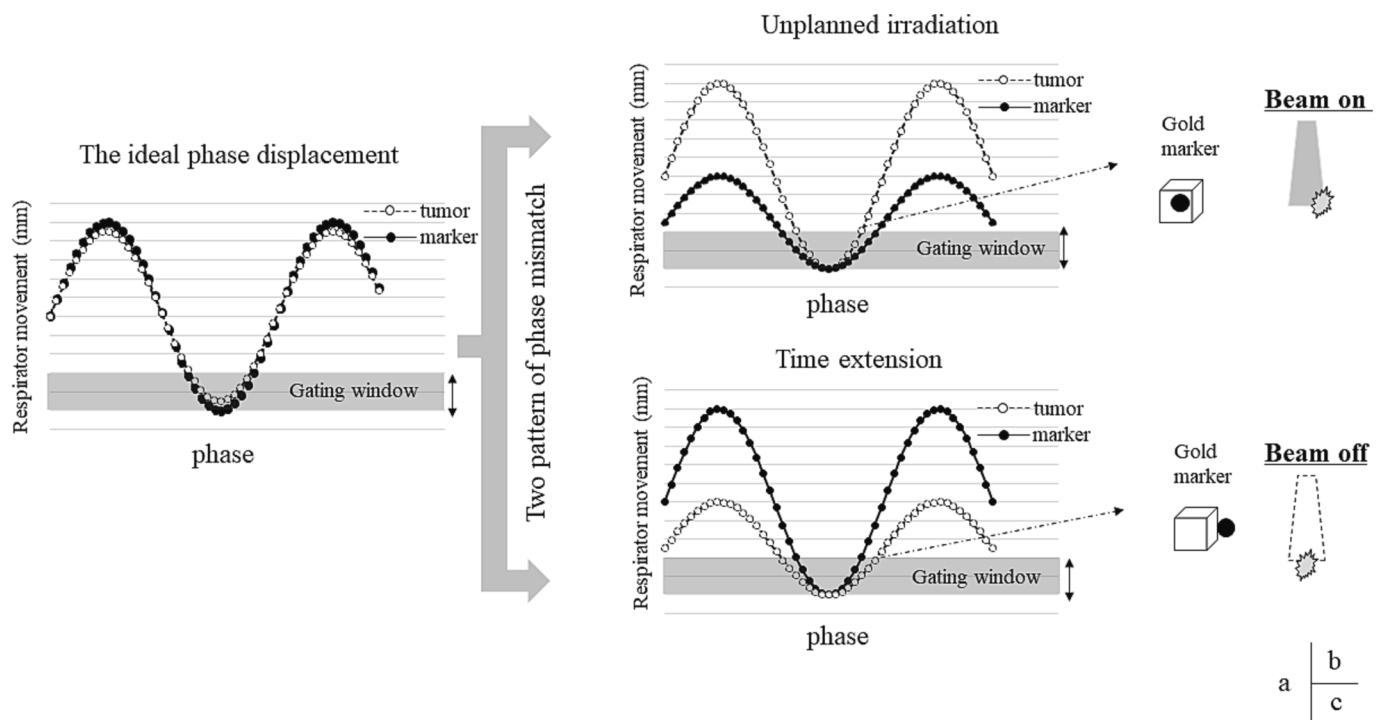

Fig. 1. Outline of this study: (a) ideal amplitude difference between the lung tumor and fiducial marker; (b) outline of unplanned irradiation; and (c) outline of the extended irradiation time.

fiducial markers were visually corrected by a radiologist owing to an incomplete contoured result.

2.3. Calculation of 3D distance between lung tumors and fiducial markers

The spatial coordinate distances were calculated from the center of gravity coordinates between the lung tumor in the anterior–posterior (AP), left–right (LR), and superior–inferior (SI) directions (AP_t, LR_t, and SI_t) and fiducial markers (AP_m, LR_m, and SI_m). The 3D distance between the lung tumor and fiducial marker at 50 % respiratory phase was then calculated using the following equation:

$$3D \ distance = \sqrt{(AP_t - AP_m)^2 + (LR_t - LR_m)^2 + (SI_t - SI_m)^2} \qquad (1)$$

Then, the 3D distance of the respiratory movement of the lung tumor and fiducial markers on 4DCT images was calculated, with the 50 % respiratory phase image as the reference, according to the following equations:

$$3D \ distance \ of \ the \ lung \ tumor = \sqrt{(AP_{t0\%} - AP_{t50\%})^2 + (LR_{t0\%} - LR_{t50\%})^2 + (SI_{t0\%} - SI_{t50\%})^2} \qquad (2)$$

$$3D \ distance \ of \ the \ fiducial \ marker = \sqrt{(AP_{m0\%} - AP_{m50\%})^2 + (RL_{m0\%} - RL_{m50\%})^2 + (SI_{m0\%} - SI_{m50\%})^2} \qquad (3)$$

Equations (2) and (3) were used to calculate the 3D distance of the respiratory movement of the lung tumor and fiducial markers, respectively, for all other phases.

2.4. Evaluation of the relationship between the spatial coordinates of the lung tumor and fiducial markers and the phase difference of respiratory movement

The cross-correlation coefficients of the respiratory movement of the spatial coordinates (LR, SI, AP, and 3D directions) between the lung tumor and fiducial markers were calculated using the following equation:

$$Cross - correlation \ coefficient \ (X, Y) = \frac{\sum(x - \bar{x}) \sum(y - \bar{y})}{\sqrt{\sum(x - \bar{x})^2 \sum(y - \bar{y})^2}}$$

where x and y are discrete data points of the phase and position in each direction, respectively, for the lung tumor and fiducial markers.

Moreover, the cross-correlation coefficients between the lung tumor and respiratory movement of the fiducial markers were evaluated separated by tumor regions (upper lobe, 15 patients; middle and lower lobe, 16 patients), and the lower and upper 95 % confidence intervals and differences in statistical significance in each direction were evaluated.

2.5. Calculation of respiratory movement and amplitude difference between the lung tumor and fiducial markers for each gating window

The cases with extended irradiation time and unplanned irradiation were evaluated for the amplitude differences between the lung tumor and fiducial markers within the gating window. The amplitude within each gating window of ≤ 1, ≤ 2, and ≤ 3 mm per direction of the fiducial marker was determined for evaluating the 3D distance between the tumor and marker based on 50 % of the respiratory movement between the tumor and the fiducial marker. The phase number of fiducial markers within each gating window was compared with the phase number of lung tumors within each gating window. Unplanned irradiation was calculated as a negative value (the respiratory movement of the lung tumor outside the gating window and the respiratory movement of the fiducial marker within the gating window) of the phase difference, whereas extended irradiation time was calculated as a positive value (the respiratory movement of the fiducial marker outside the gating window and the respiratory movement of the lung tumor within the gating window) of the phase difference. For each gating window of the fiducial marker (≤ 1, ≤ 2, and ≤ 3 mm), the percentage of phase numbers that resulted in extended irradiation time and unplanned irradiation was calculated.

2.6. Respiratory movement relationships among lung tumors, fiducial markers, and radiotherapy dose

Radiotherapy treatment plans with an isotropic PTV margin of 5 mm based on the 50 % phase CT images were used to evaluate dose changes in cases of unplanned irradiation using RTPS. First, for each fiducial marker in all patients, the isocenter was shifted by the respiratory movement of the lung tumor and fiducial markers in LR, SI, and AP positions. Next, the PTV mean dose of the lung tumor was calculated by shifting the isocenter and averaged in all phases. The rate of decrease in the PTV mean dose of the unplanned irradiation was calculated by comparing it with the planned PTV mean dose.

2.7. Statistical analyses

The statistical software JMP Pro version 15 (SAS Institute, Cary, NC) was used to perform statistical analysis. Correlation coefficients (r) were obtained using multivariate analysis. The statistical significance of changes in the respiratory movement between the lung tumor and fiducial marker observed was assessed with a Mann–Whitney U test. Results were considered significant at a p value of < 0.001.

3. Results

The median (minimum–maximum) distance of the spatial coordinates between the lung tumor and fiducial markers was 2.8 cm (0.5–9.3 cm) in the 3D direction, 1.6 cm (0.0–7.0 cm) in the LR direction, 1.2 cm (0.1–4.9 cm) in the SI direction, and 1.0 cm (0.0–4.4 cm) in the AP direction.

The coefficient of determination (r^2) between the 3D distance and cross-correlation coefficients of respiratory movement between the lung tumor and fiducial marker was as follows: LR, 0.03; AP, 0.01; SI, 0.01; and 3D, 0.01. The results of the cross-correlation coefficients of respiratory movements showed no correlation with the distance between the lung tumor and fiducial marker.

Fig. 2 and Table 1 show the relationship between the cross-correlation coefficients of respiratory movements between the lung tumor and fiducial marker in each direction for the upper (UG) and middle and lower lobe groups (MLG). The mean $\pm$ standard deviation cross-correlation coefficients of respiratory movements between the lung tumor and fiducial markers in all patients were 0.65 ± 0.28 for LR, 0.78 ± 0.26 for AP, 0.80 ± 0.31 for SI, and 0.92 ± 0.11 for 3D, with the
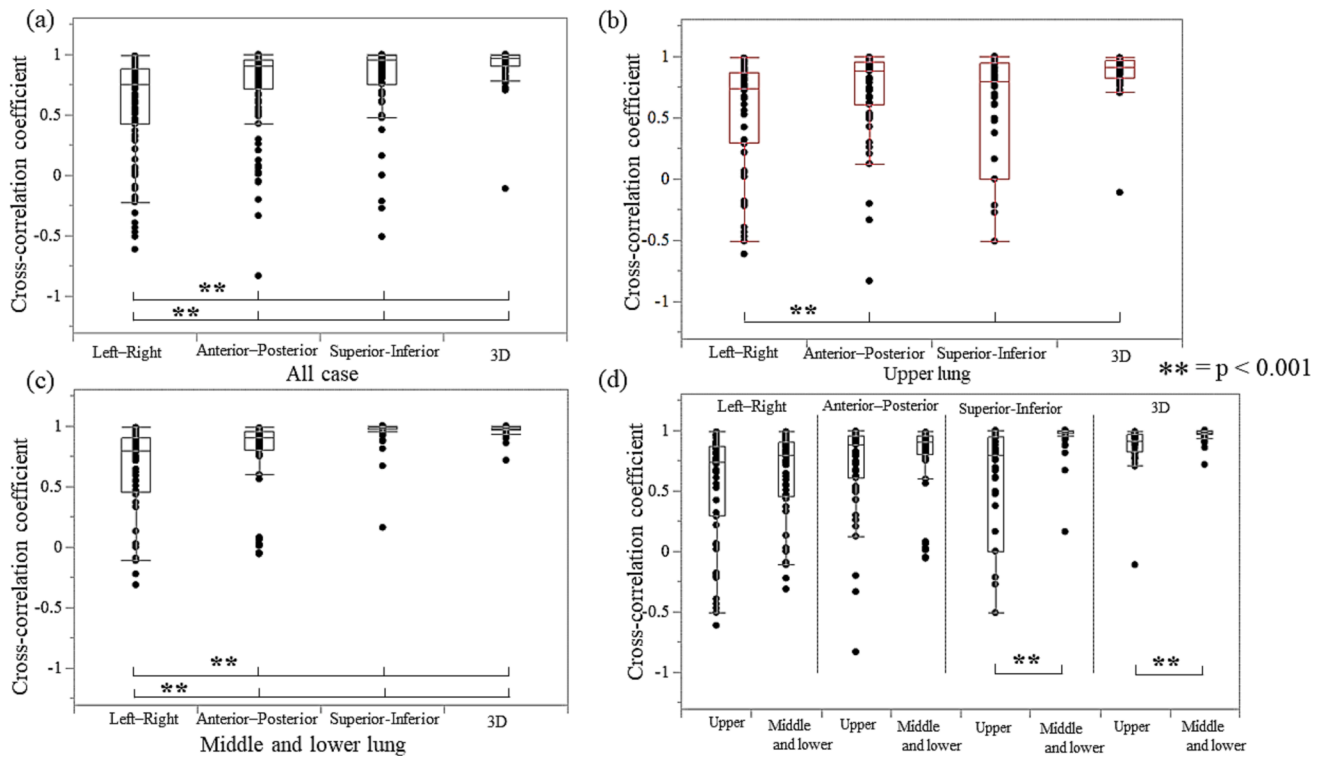
Fig. 2. Relationship of the cross-correlation coefficient of respiratory movement and each lung region: (a) all cases (significant difference), and the region groups of the (b) upper lobe, (c) middle and lower lobes, and (d) upper lobe versus the middle and lower lung. The nonparametric Mann–Whitney *U* test was used to evaluate significance ($p < 0.001$).

Table 1

Cross-correlation coefficients between lung tumors and fiducial markers in each lung region.

Region	Direction	Mean maximum movement (cm)		Cross-correlation coefficients between lung tumors and fiducial markers		
		Tumor	Fiducial marker	Mean (SD)	Lower 95 % CI	Upper 95 % CI
	LR	0.5	0.7	0.52 (0.46)	0.39	0.65
Upper lobe	AP	1.3	1.1	0.71 (0.37)	0.6	0.81
	SI	2.3	2.0	0.59 (0.44)	0.47	0.71
	3D	3.7	2.9	0.88 (0.16)	0.83	0.92
	LR	1.2	1.2	0.63 (0.36)	0.53	0.73
Middle and lower lobes	AP	1.5	2.1	0.79 (0.30)	0.7	0.87
	SI	12.1	13.0	0.95 (0.12)	0.92	0.98
	3D	12.4	13.6	0.97 (0.05)	0.95	0.98
	LR	1.1	0.1	0.65 (0.28)	0.60	0.70
All	AP	1.5	1.5	0.78 (0.26)	0.73	0.83
	SI	6.5	6.0	0.80 (0.31)	0.74	0.86
	3D	6.8	6.7	0.92 (0.11)	0.90	0.94

LR, left–right; AP, anterior–posterior; SI, superior–inferior; 3D, three-dimensional; SD, standard deviation; CI, confidence intervals.

3D direction having the highest mean cross-correlation coefficient (Table 1). In the UG, significant differences were found between SI and 3D, whereas no significant differences were found between SI and 3D in the MLG. A characteristic trend of high correlation in the SI direction was observed in the MLG compared with the UG (Fig. 2 (d), Table 1).

The percentage of phase numbers resulting in extended irradiation time (mismatch phase > 0) and unplanned irradiation (mismatch phase < 0) was 71 % and 11 %, 41 % and 28 %, and 11 % and 63 % for the gating windows ≤ 1, ≤ 2, and ≤ 3 mm, respectively (Fig. 3). A significant difference in the mismatch of phases between the lung tumor and fiducial marker in all gating window settings was noted ($p < 0.001$, Mann–Whitney *U* test). In 3 of the 31 cases, unplanned irradiation could be avoided by changing the fiducial marker and gating window, i.e., the gating window had to be changed from ≤ 2 mm to ≤ 1 mm.

The difference between the PTV mean doses of planned and unplanned irradiations increased by widening the gating window (Fig. 4). The ≤ 3-mm gating window was significantly different than the ≤ 1- and ≤ 2-mm gating windows ($p < 0.001$, Mann–Whitney *U* test). However, the PTV mean dose decreased by 2 % for all gating windows in unplanned irradiation (Fig. 4).

Fig. 5 shows four cases with varying amplitude differences between the lung tumor and fiducial marker. The respiratory movement of the fiducial marker and lung tumor coincided within the ≤ 2-mm gating window (Fig. 5a), and the amplitude difference between the lung tumor and fiducial marker was 0 within the ≤ 2-mm gating window. Fig. 5b shows a case of unplanned irradiation. Fig. 5c shows a case of unplanned irradiation in which changing the gating window from ≤ 2 mm to ≤ 1 mm did not prevent unplanned irradiation. A case of extended irradiation time, which was shortened by changing the gating window from ≤ 2 mm to ≤ 3 mm, is shown in Fig. 5d.

4. Discussion

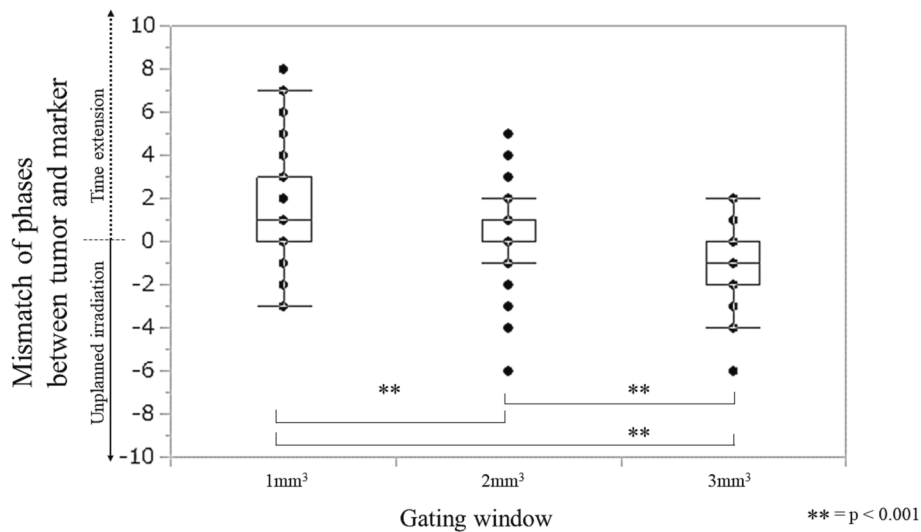This study evaluated the effect of the differences in respiratory

Fig. 3. Evaluation of the difference between the fiducial marker gating windows. Mismatch of phases between the tumor and marker for each marker gating window (≤ 1, ≤ 2, and ≤ 3 mm). A significant difference was observed for all marker gating windows (equal-variance Mann–Whitney U test; $p < 0.001$).
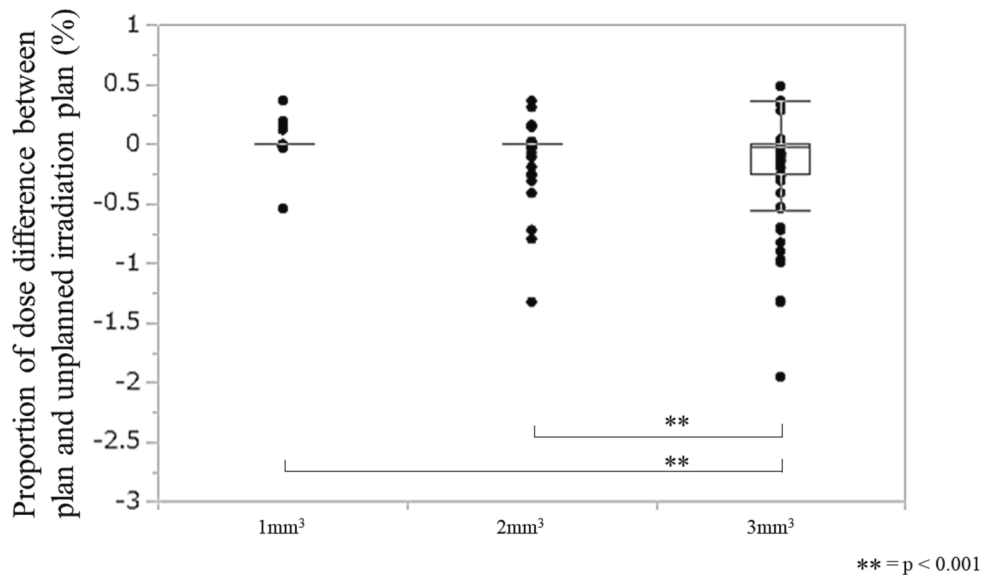

Fig. 4. Dose decrease rate as a function of selecting the mismatch marker between the tumor and marker: the relationship between the marker gating window and the decrease rate, which reflects the difference between the PTV mean doses of planned and unplanned irradiations. The nonparametric Mann–Whitney U test was used to evaluate significance ($p < 0.001$).

movement between the fiducial marker, which serves as a surrogate tumor marker, and the lung tumor. No correlation was found between the lung tumor-to-fiducial marker distance and the respiratory movement in each direction, which, in our opinion, indicates that the lung tumor-to-fiducial marker distance is not an appropriate index for selecting fiducial markers in treatment planning CT[12]. As shown in Fig. 5, the movement of the fiducial marker and lung tumor varies among patients, and in lung SBRT, a mismatch in the respiratory movement between the lung tumor and fiducial markers can lead to prolonged and erroneous irradiation [13]. Therefore, it is important to evaluate the respiratory movement relationship between the fiducial marker and lung tumor using 4DCT before treatment and select an optimal fiducial marker with the highest correlation among all markers [14].

The correlation coefficients between lung tumors and fiducial markers in all cases demonstrate some negative correlations in all directions (Fig. 2), indicating that the respiratory movement of fiducial

markers close to the lung tumor was different [5,15]. The SI direction and 3D distance significantly differed between the UG and MLG, and we considered that the SI direction has a high correlation because the middle and lower lobes near the diaphragm tend to get affected by respiratory movement [14].

Narrowing the gating window of the fiducial marker increased the treatment time, whereas widening the gating window increased the risk of unplanned irradiation. Therefore, we believe that the gating window should not be fixed and that the lung tumor and individual markers should be preliminarily evaluated using 4DCT or other methods for individual patients [16]. In actual treatment, multiple fiducial markers are often implanted, and we believe that selecting an appropriate fiducial marker among all markers with few amplitude differences, in advance, can help avoid unplanned irradiation.

To avoid unplanned irradiation in lung dynamic body-tracking SBRT, it is effective to use a fiducial marker with a respiratory shift larger than that of the lung tumor within the gating window setting
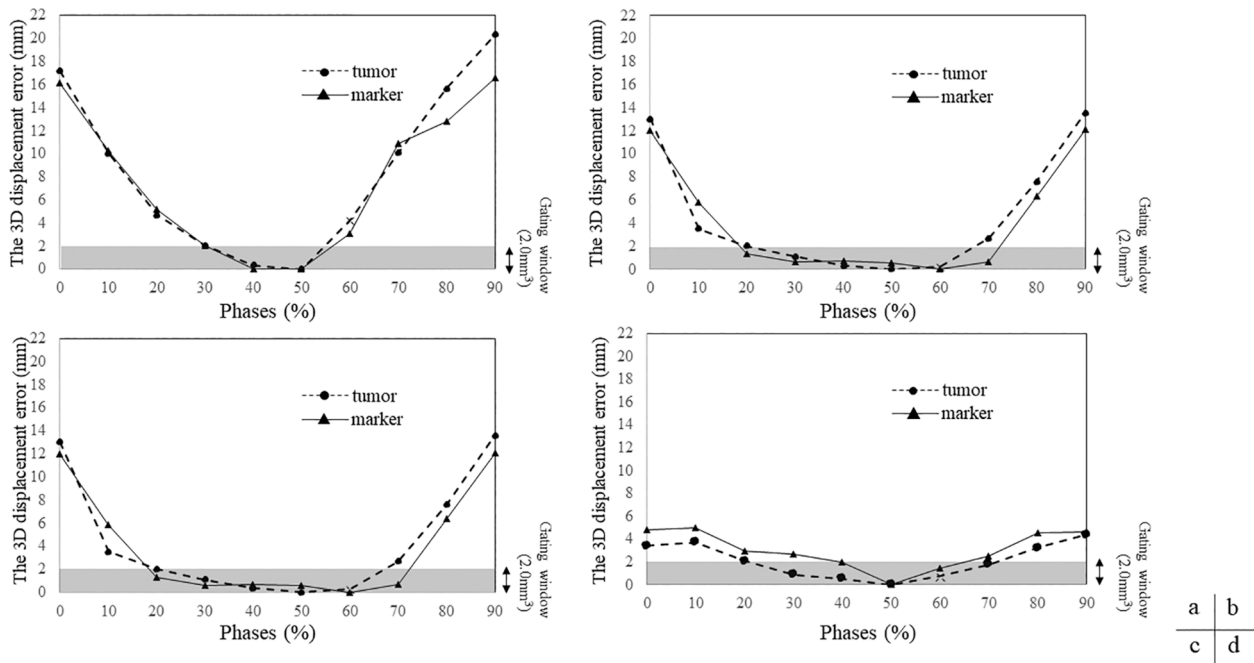
Fig. 5. Relationship of the amplitude difference between a typical lung tumor and fiducial marker: clinical cases are shown for (a) no difference in the amplitude between the lung tumor and fiducial marker, (b) unplanned irradiation of the lower lobe group, (c) unplanned irradiation of the middle and upper lobe group, and (d) extended irradiation time in the lower lobe group.

(Fig. 5b). However, extended irradiation time poses the risk of position displacement from the start of irradiation because of holding the body position and due to respiratory variation during treatment [6]. Therefore, the amplitude difference between the fiducial marker and lung tumor should be evaluated in advance using 4DCT (or other techniques), although changing the gating window is one of the options for performing the treatment accurately in a short time.

For evaluating the changes in the planned dose with a change in the distance of the respiratory movement between the lung tumor and fiducial marker, the PTV mean dose for the ≤ 1-, ≤ 2-, and ≤ 3-mm gating windows decreased by 2 %, which is an acceptable dose difference according to the guidelines and other studies [6,17]. In this study, the planned PTV margin was isotopically 5 mm, which may be one reason why the amount of theoretical shift alone did not cause a large dose difference. However, the PTV mean dose of the ≤ 3-mm gating window was statistically significantly different from that of the ≤ 1-mm and ≤ 2-mm gating windows. In addition, widening the gating window may increase unplanned irradiation and dose differences between the planned and actual doses. Because of residual errors, such as marker position movement and setup errors during actual treatment [18], we believe that the amplitude difference between the lung tumor and fiducial marker should be minimized within the gating window.

A limitation of this study is the statistical uncertainty due to the small sample size. Studies with larger samples are necessary to obtain an accurate correlation between the 3D distance of the fiducial marker and lung tumor. In addition, this study evaluated the amplitude difference between the lung tumor and fiducial markers using 4DCT, which may include uncertain underestimations and overestimations of respiratory movements and resolution limits of the phase numbers via 4DCT [19]. The spatial coordinates of the fiducial marker may be displaced during SBRT, and the amplitude difference between the lung tumor and fiducial marker should be observed during SBRT [20]. In the future, we believe that more robust and dynamic tracking during SBRT may be realized by combining magnetic resonance imaging and respiration by lung volume in addition to fiducial marker [9,12,21,22].

In conclusion, this study showed no correlation between the distance from the lung tumor to fiducial marker and respiratory movement in each direction. In addition, the distance of the respiratory movement of individual fiducial markers and the lung tumor led to unplanned irradiation and extended irradiation times. By analyzing the patient-specific respiratory movement of a lung tumor and fiducial markers using 4DCT in advance, unplanned irradiation can be avoided by adjusting the gating window.

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None.
Role of funding source
None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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