



Development of a Margin Determination Framework for Tumor-Tracking Radiation Therapy With Intraoperatively Implanted Fiducial Markers

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Purpose: To develop an internal target volume (ITV) margin determination framework (or decision-supporting framework) for treating multiple lung metastases using CyberKnife Synchrony with intraoperatively implanted fiducial markers (IIFMs). The feasibility of using non-ideally implanted fiducial markers (a limited number and/or far from a target) for tracking-based lung stereotactic ablative radiotherapy (SABR) was investigated.

Methods: In the developed margin determination framework, an optimal set of IIFMs was determined to minimize a tracking uncertainty-specific ITV (ITV_{tracking}) margin (margin required to cover target-to-marker motion discrepancy), i.e., minimize the motion discrepancies between gross tumor volume (GTV) and the selected set of fiducial markers (FMs). The developed margin determination framework was evaluated in 17 patients with lung metastases. To automatically calculate the respiratory motions of the FMs, a template matching-based FM tracking algorithm was developed, and GTV motion was manually measured. Furthermore, during-treatment motions of the selected FMs were analyzed using log files and compared with those calculated using 4D CTs.

Results: For 41 of 42 lesions in 17 patients (97.6%), an optimal set of the IIFMs was successfully determined, requiring an ITV_{tracking} margin less than 5 mm. The template matching-based FM tracking algorithm calculated the FM motions with a sub-millimeter accuracy compared with the manual measurements. The patient respiratory motions during treatment were, on average, significantly smaller than those measured at simulation for the patient cohort considered.

Conclusion: Use of the developed margin determination framework employing CyberKnife Synchrony with a limited number of IIFMs is feasible for lung SABR.

Keywords: lung metastasis, intraoperative fiducial marker implantation, CyberKnife Synchrony, fiducial tracking, internal target volume, stereotactic ablative radiotherapy

INTRODUCTION

CyberKnife Synchrony, a fiducial-based tracking method, is an attractive radiation treatment (RT) modality with CyberKnife's dosimetric advantages due to non-coplanar delivery of radiation doses (1). In general, CyberKnife Synchrony requires fiducial marker (FM) implantation prior to RT simulation and planning, which is mainly performed *via* a percutaneous, computed tomography (CT)-guided insertion procedure. Moreover, FMs can be inserted during surgery (2). Intraoperative FM implantation can be beneficial in some clinical situations, in which the extent of surgery is limited by concerns on morbidity or pulmonary function. In this case, the remaining unresectable lesions can be treated *via* stereotactic ablative radiotherapy (SABR) with intraoperatively implanted FMs (IIFMs). Furthermore, when a "missing lesion" exists (3), which is not detectable during surgery, FMs can be intraoperatively implanted and used for the following SABR. In addition to the use of IIFMs, existing FMs that were used in previous treatments can be further utilized for additional RT.

These challenging clinical scenarios, in which a limited number of FMs are available, including those located far from a target, pose the following clinical questions because inserting three to five FMs near each radiation target is ideal for the CyberKnife fiducial tracking-based RT: 1) which among the various RT techniques, including CyberKnife fiducial tracking, respiratory gating, and internal target volume (ITV)-based technique, is the optimal treatment?, 2) if a lesion is treated using CyberKnife fiducial tracking, how can the uncertainty related to motion discrepancy between the target and existing FMs be quantified for consideration in treatment planning?

Therefore, to address the aforementioned and unanswered questions, we aimed to develop a margin determination framework (a decision-supporting framework) and evaluate its clinical feasibility. Specifically, this study evaluated the feasibility of using the developed margin determination framework for treating multiple lung metastases using IIFMs. To the best of the authors' knowledge, this study is the first to make an effort towards developing such a novel framework, which has the potential to facilitate usage of non-ideally implanted FMs for tracking-based RT, thereby reducing the risk of side effects by additional FM implantation. Furthermore, successful implementation of the developed framework can facilitate multi-site SABR using a limited number of FMs as dynamic transition into repeat oligometastatic and induced oligometastatic diseases may be possible depending on the response to local or systemic therapy (4).

METHODS AND MATERIALS

ITV_{tracking} Margin Determination Framework

The developed margin determination framework was designed to 1) analyze the motions of a radiation target and IIFMs,

Abbreviations: ITV, internal target volume; IIFM, intraoperatively implanted fiducial marker; SABR, stereotactic ablative radiotherapy; FM, fiducial marker; CT, computed tomography; I-S, inferior-superior; CPAP, continuous positive airway pressure; GTV, gross tumor volume; CK, CyberKnife; R-L, right-left; A-P, anterior-posterior; VMAT, volumetric-modulated arc therapy; PTV, planning target volume.

2) evaluate the motion synchronization level between the target and all possible sets of the IIFMs, and 3) suggest an optimal FM set S^* showing maximum synchronization with an additional margin required to cover the target-to-marker motion discrepancy. This additional margin is referred to as "tracking uncertainty-related ITV (ITV_{tracking}) margin" in this study. The margin determination framework was developed using MATLAB (MathWorks, Natick, MA, USA). The steps in the developed framework can be mathematically formulated as follows:

$$S^* = \arg \min f(S), \quad S \subset \{1, 2, \dots, N_F\} \quad (1)$$

$$f(S) = \|\mathbf{u}_T - \mathbf{u}_S\|_2 \quad (2)$$

where $f(S)$ represents the root mean square difference between the target motion \mathbf{u}_T and the average motion \mathbf{u}_S of a subset of the FMs S , and N_F represents the number of the IIFMs. Finally, ITV_{tracking} margin is defined as follows:

$$\text{ITV}_{\text{tracking}} \text{ margin} = \|\mathbf{u}_T - \mathbf{u}_{S^*}\| \quad (3)$$

Fiducial Marker Tracking Algorithm

A template matching-based registration algorithm was developed to calculate the motions of each of the IIFMs in 4D CT using ITK (5). FMs were initially detected by thresholding HU values ($\text{HU} > 1500$). Then, a template matching algorithm was used to find an optimal translation vector that maximizes a mutual information (6–8) between the reference (0% phase) and target (10–90% phases) images. A template was defined as a cubic region of $4 \times 4 \times 10 \text{ mm}^3$ centered at the detected FM on the reference image; the dimension of the cubic region-of-interest was optimally determined by a parametric study. Multi-resolution template matching was performed by starting with a grid size of 1.0 mm and reducing the grid spacing to 0.25 mm.

Phantom Study

A phantom study was conducted to evaluate the feasibility of using 4D CT and the developed registration-based FM tracking method for the calculation of FM motion. The FM motions on 4D CT images were analyzed using two methods, manual and automatic (template matching-based), and were compared with the known motions. A Quasar Respiratory Motion Phantom (Modus QA, London, Ontario, Canada) was used to simulate a respiratory motion (9), expressed by $z(t) = z_0 - b \cos^4(\pi t/\tau)$, where $z(t)$ and z_0 represent the inferior-superior (I-S) location of the target at time t and initial position, respectively, b represents the peak-to-peak motion amplitude, and τ represents the respiration cycle ($b = 5, 10, 15,$ and 20 mm ; $\tau = 4 \text{ s}$). Three gold FMs (approximately 1 mm diameter and 3 mm length) were inserted into a Cedar Lung Tumour Insert (Modus QA, London, Ontario, Canada). Ten-phase 4D CTs of the phantom were acquired using a Toshiba Aquilion CT simulator (Toshiba Medical System, Japan) and Abches (APEX Medical, Inc., Japan), a respiration-monitoring device, with a slice thickness of 3 mm. It is noted that this 4D CT acquisition protocol used for

the phantom was the same as that in the patient 4D CT acquisition.

Patient Study

Seventeen patients with lung metastases and IIFMs were considered for a retrospective analysis approved by the institutional review board of Severance Hospital, Seoul, South Korea (4-2021-0440). Characteristics of the patients are summarized in **Table 1**. The number of lung lesions varied among the patients (range: 1 to 9). Two to six FMs (median: 5) were implanted for each patient during surgery performed prior to the RT of the lung metastases. Maximally, three FMs were implanted into each side of the lungs, resulting in a total of six FMs. **Figure 1** presents a patient case with six IIFMs. As illustrated in **Figure 1**, in general, one FM was implanted into each of the upper, middle, and lower lobes on each side the lungs (in total, 73 IIFMs for 17 patients). Lung lesions of the patient cohort were treated with one of the following dose-fractionation schemes: 20 Gy \times 1, 25 Gy \times 1, 30 Gy \times 1, 18 Gy \times 3, and 6 Gy \times 5. Continuous positive airway pressure (CPAP) with a pressure of 12–17 cmH₂O (median: 15 cmH₂O) was used for respiration motion management as it has been shown to effectively reduce radiation dose to the lung (10–12).

The developed margin determination framework was tested for the patient data. For each of the lung targets, the motion-to-marker motion discrepancies were analyzed, finally resulting in an optimal set of IIFMs with a corresponding ITV_{tracking} margin. The accuracy of the developed FM tracking algorithm was evaluated by comparing the automatically registered motions with the manually measured motions for all the 73 FMs.

The feasibility of the developed margin determination framework was further evaluated by comparing the motions of the IIFMs calculated using the 4D CT with the in-treatment motions calculated using treatment log files. Using the three-

dimensional coordinates of the FMs tracked during the treatment beam delivery (average motion of the FMs), motion amplitudes during each treatment fraction were calculated. A paired two-tailed t-test with 95% confidence was conducted using MATLAB to evaluate the hypothesis that the pretreatment and average in-treatment motions of the FMs were statistically different.

RESULTS

ITV_{tracking} Margin Calculation

Figure 2A illustrates how the developed framework determined an optimal FM set with a minimal ITV_{tracking} margin. Consequently, for patient 5, to treat the GTV with the FM R2, ITV_{tracking} margins of 0.5, 2.7, and 2.7 mm were required to cover the GTV-to-marker motion discrepancies in the right-left (R-L), anterior-posterior (A-P), and I-S directions, respectively.

The ITV_{tracking} margins calculated across all of the lung lesions were 1.0 \pm 0.8, 1.1 \pm 1.2, and 1.8 \pm 1.7 mm in the R-L, A-P, and I-S directions, respectively (see **Figures 2B–D**). Of the 42 lung lesions, only one required an ITV_{tracking} margin larger than 5 mm (8.4 mm in the I-S direction for patient 7). This lesion was treated with a volumetric-modulated arc therapy (VMAT) plan with the ITV technique. Detailed information (selected FMs, corresponding ITV_{tracking} margins, and GTV-to-marker distances) of the ITV_{tracking} determination results for all lung lesions is summarized in **Table 2**. The GTV-to-marker distance was 59.3 \pm 24.6 mm.

The locations of the IIFMs for each patient are shown in a coronal view in **Figure 3**. In **Figure 4**, the locations of the IIFMs for all patients are approximately plotted with the lungs of representative dimensions and are color-coded depending on the FM motion amplitudes.

TABLE 1 | Summary of patient characteristics.

Patient #	Number of GTVs			Number of fiducial markers			Number of CK plans	Number of log-available CK plans
	Right	Left	Total	Right	Left	Total		
1	6	3	9	3	2	5	9	8
2	1	0	1	3	0	3	1	1
3	0	2	2	3	2	5	2	2
4	0	1	1	3	2	5	1	1
5	1	0	1	2	2	4	1	1
6	4	0	4	3	3	6	4	3
7	1	0	1	2	1	3	0	0
8	3	1	4	2	1	3	4	3
9	2	0	2	2	2	4	2	2
10	1	0	1	1	1	2	1	0
11	1	1	2	2	2	4	2	2
12	1	0	1	3	0	3	1	1
13	1	0	1	3	2	5	1	1
14	2	2	4	3	3	6	4	4
15	1	0	1	3	2	5	1	1
16	4	1	5	3	2	5	5	1
17	2	0	2	3	2	5	2	0
Total	31	11	42	44	29	73	41	31

GTV, gross tumor volume; CK, CyberKnife.

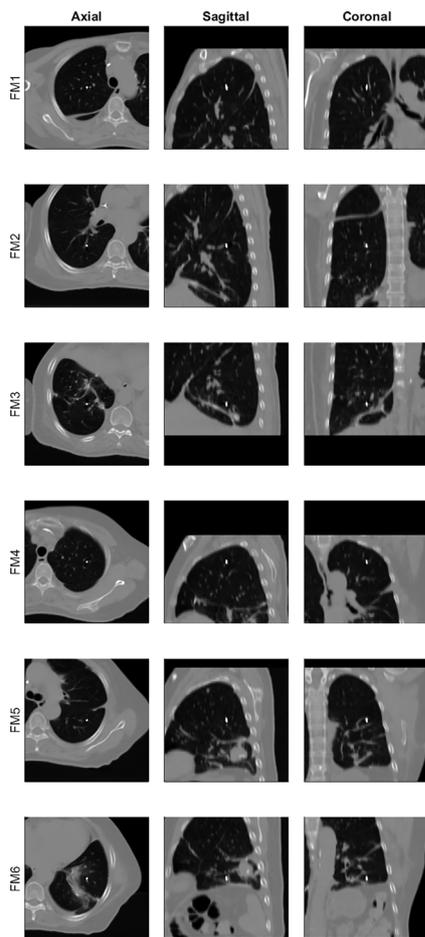


FIGURE 1 | Example of intraoperatively implanted fiducial markers (six markers for patient 14), each of which is displayed at the center of the axial (first column from left), sagittal (second), and coronal (third) views.

Accuracy of Fiducial Tracking Algorithm: Phantom

Figure 5 presents the comparison results of the FM motions calculated using manual and automatic localization methods with the ground truth motions. The manually segmented and registered motions agreed reasonably well with each other, resulting in a difference of 0.2 ± 0.2 mm. The automatically measured motions were smaller than the ground truth motions by, on average, 0.5, 0.3, 0.5, and 1.8 mm for the 5-, 10-, 15-, and 20-mm reference motions, respectively.

Accuracy of Fiducial Tracking Algorithm: Patient

The registration errors, which were calculated as the difference between the registered and manually segmented FM positions, are plotted as histograms in **Figure 6**. The absolute registration errors were 0.1 ± 0.1 , 0.1 ± 0.1 , and 0.3 ± 0.3 mm in the R-L, A-P, and I-S directions, respectively, in all patients. In 12 (1.8%) of the 657 alignments, the registration error was larger than 2 mm in

the I-S direction. These relatively large misalignments occurred for the image registrations from 0% to intermediate phases where FMs quickly moved and are thereby abnormally displayed.

The differences between the motion amplitudes that were manually measured and calculated using the template matching algorithm across all the FMs of patients were 0.1 ± 0.1 (range: -0.6 to 0.6), 0.1 ± 0.1 (-0.5 to 0.5), and 0.2 ± 0.2 (-0.9 to 0.9) mm in the R-L, A-P, and I-S directions, respectively.

Log-Based In-Treatment Motion Analysis

Figure 7 presents paired box plots comparing the pretreatment and mean in-treatment motion amplitudes, which were analyzed using 4D CT and the treatment log file, respectively. The mean in-treatment motion amplitudes were smaller than the pretreatment motion amplitudes, resulting in statistically significant differences of -0.5 ± 0.5 , -1.1 ± 1.3 , and -1.0 ± 2.0 mm in the R-L, A-P, and I-S directions, respectively ($p < 0.005$ in all directions).

DISCUSSION

This study demonstrated the feasibility of using the developed ITV_{tracking} margin determination framework to aid in the decision-making process of treating multiple lung metastases using IIFMs. An optimal set of IIFMs was successfully determined for each of the GTV of the patient cohort. An ITV_{tracking} margin of less than 5 mm was required for 41 of 42 patients to cover the motion discrepancy between the GTV and selected FMs. Patient 1, in whom nine lung lesions were defined, is the best example that shows the effectiveness of the IIFM-based RT technique. Without the insertion of FMs during surgery, treating this large number of lung metastases was not practically feasible, requiring implantation of at least 27 FMs for an ideal tracking. However, with the developed framework, nine lung metastases were treated with only five IIFMs by introducing reasonable margins.

To the best of our knowledge, this study is the first to develop an innovative margin determination framework that can facilitate SABR of multiple lung metastases using IIFMs although the clinical relevance of these results is yet to be elucidated and will be reported separately. This novel development suggests a technological combination that supports a challenging treatment, which is performed mainly in an oligo-metastatic setting. First, as suggested by Pop et al. (2), FM placement during surgery can be a promising method to treat potential local recurrence without percutaneous or bronchoscopic insertion. Second, treating multiple lung metastases can be further supported by superior dosimetric characteristics (1) of the CyberKnife plans because of its non-coplanar beam arrangement. Finally, CPAP can reduce the radiation dose to the lungs (10–12). The combination of the aforementioned treatment techniques can facilitate the ablative treatment of multiple lung metastases.

Both phantom and patient studies demonstrated that gold FMs can be localized using the developed fiducial tracking algorithm with a sub-millimeter accuracy despite the limited resolution of 4D CT images (3 mm slice thickness in this study). The motions calculated using the template matching-based fiducial tracking algorithm closely coincided with those manually

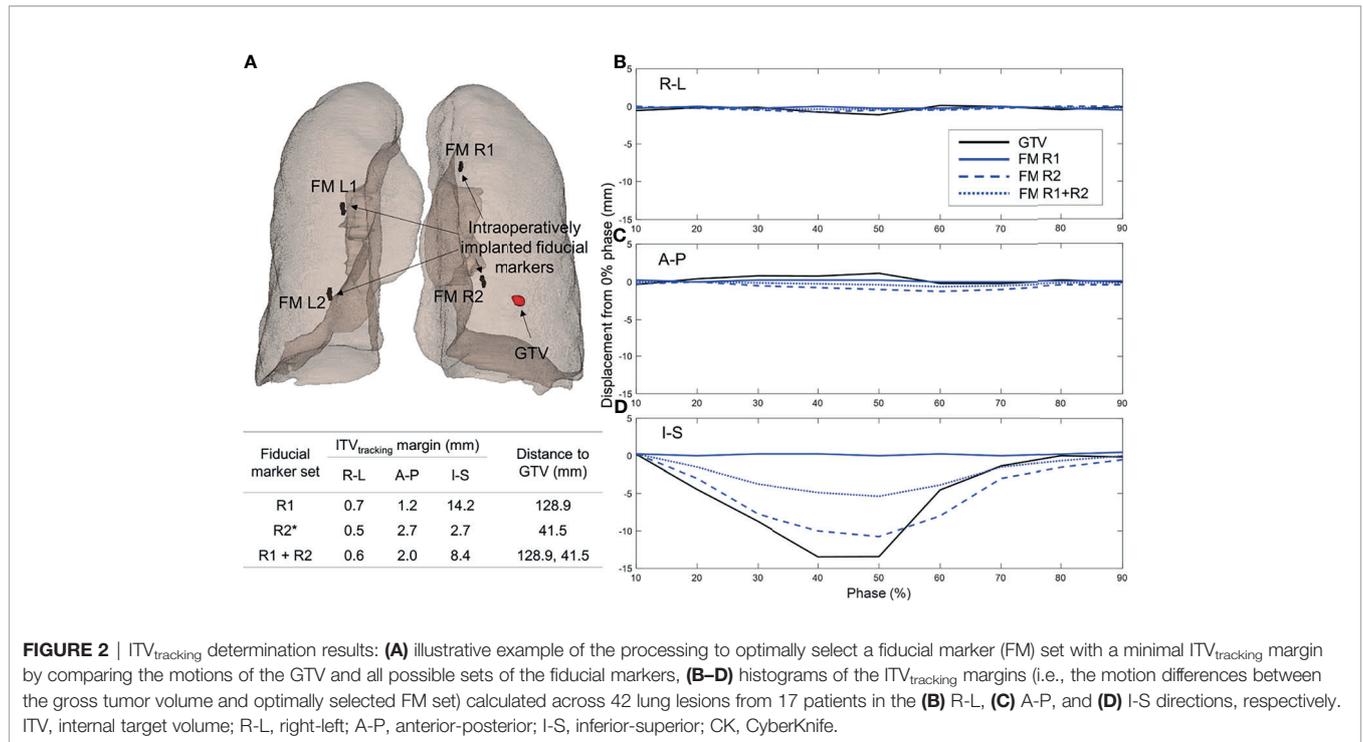


FIGURE 2 | ITV_{tracking} determination results: (A) illustrative example of the processing to optimally select a fiducial marker (FM) set with a minimal ITV_{tracking} margin by comparing the motions of the GTV and all possible sets of the fiducial markers, (B–D) histograms of the ITV_{tracking} margins (i.e., the motion differences between the gross tumor volume and optimally selected FM set) calculated across 42 lung lesions from 17 patients in the (B) R-L, (C) A-P, and (D) I-S directions, respectively. ITV, internal target volume; R-L, right-left; A-P, anterior-posterior; I-S, inferior-superior; CK, CyberKnife.

TABLE 2 | Summary of the ITV_{tracking} determination results for each of the 42 lung lesions for 17 patients.

Patient #	GTV #	Optimal FM set	ITV _{tracking} margin (mm)			GTV-to-FM distance (mm)	
			R-L	A-P	I-S		
1	Right	1	R3	0.7	0.2	1.0	30.9
		2	R2, R3	1.4	0.9	0.6	69.7, 20.3
		3	R2, R3	0.9	0.6	0.7	42.7, 33.9
		4	R1	1.2	2.8	3.8	103.7
		5	R2, R3	1.3	0.5	0.8	18.7, 68.5
		6	R1, R2	1.0	0.7	1.3	90.4, 38.8
2	Left	1	L1, L2	3.2	0.9	0.3	52.7, 59.3
		2	L1, L2	0.7	0.8	2.0	100.8, 11.1
		3	L2	3.3	4.1	4.3	42.0
3	Right	1	R2	0.4	0.1	0.4	67.9
2		L1	0.9	1.9	2.1	39.4	
4	Left	1	L2	1.0	1.2	2.9	63.0
		2	L2	1.2	0.2	2.9	20.8
5	Right	1	R2	0.5	2.7	2.7	41.5
6	Right	1	R1	0.8	0.1	4.8	45.5
		2	R1, R2	1.5	0.8	0.4	128.5, 52.6
		3	R3	0.3	0.1	4.9	55.6
		4	R2	0.4	0.2	0.4	47.9
7	Right	1	R2	0.4	1.1	8.4	52.4
		2	R1, R2	1.3	1.5	3.4	55.3, 66.8
		3	R1	1.0	0.5	0.2	69.2
8	Left	1	L1	0.3	0.5	0.8	82.4
		2	L1	1.0	1.5	0.1	42.8
		3	L1	1.0	1.5	0.1	42.8
9	Right	1	R1, R2	0.1	1.7	0.5	59.3, 123.8
		2	R1, R2	0.9	0.0	0.4	80.9, 91.5
10	Right	1	R1	0.6	4.2	3.8	57.5
11	Right	1	R1	0.1	0.5	4.4	96.6
12	Left	1	L1, L2	1.8	0.3	1.0	19.5, 45.0
		2	R1	0.7	0.0	0.7	20.5

(Continued)

TABLE 2 | Continued

Patient #	GTV #	Optimal FM set	ITV _{tracking} margin (mm)			GTV-to-FM distance (mm)	
			R-L	A-P	I-S		
13	Right	1	R2, R3	2.9	0.5	2.6	75.8, 63.4
14	Right	1	R3	0.9	0.9	1.2	24.0
		2	R1, R2	0.7	3.6	1.3	86.9, 52.4
	Left	1	L2	0.2	0.5	0.7	19.6
		2	L2	1.6	0.2	0.7	65.2
15	Right	1	R2, R3	0.1	0.2	1.1	31.5, 39.9
16	Right	1	R1, R2	0.4	0.7	0.7	120.1, 66.9
		2	R1, R2	1.2	0.3	0.8	132.2, 85.4
		3	R3	0.4	1.3	1.4	44.2
		4	R1, R2	1.3	0.1	0.8	146.0, 49.5
	Left	1	L1	1.7	2.3	1.4	43.3
17	Right	1	R2	0.2	4.4	1.2	92.0
		2	R1	0.5	1.8	0.8	81.2
Mean				1.0	1.1	1.8	59.3
Standard deviation				0.8	1.2	1.7	24.6

The fiducial markers were numbered in the superior-inferior direction; for instance, R1 represents the fiducial marker on the right side, which is the most superiorly located. GTV, gross tumor volume; FM, fiducial marker; R, right; L, left.

measured. However, as demonstrated in the phantom study, the motions captured in the 4D CT images (both manually and automatically detected) were similar to but slightly smaller than the ground truth motions. This motion underestimation by 4D CT may be attributed to the motion uncertainty in the phantom. For example, the insert of the phantom containing the FMs was measured to move approximately 19 mm although a motion of 20 mm was simulated. In addition, motion underestimation by 4D CT was reported in a recent study (13). As this investigation focused on the synchronization level between the lung target and IIFMs, underestimation of the respiration motions by 4D CT images may not greatly affect the resulting ITV_{tracking} margin size.

The consistency of the FM motions between simulation and treatment was evaluated using the log file information. The average in-treatment FM motions were significantly smaller than those

simulated using the planning 4D CT images. Assuming a consistent synchronization between the target and selected FMs, a smaller motion for GTVs can be theoretically expected and, therefore, a smaller motion discrepancy. In addition, relatively large standard deviations of the intrafraction motion amplitudes indicated that the patient breathed with various amplitudes over the long treatment duration with CyberKnife. Given that the in-treatment motion amplitudes were larger compared with planned motion amplitudes for a small portion of the total treatment time, only a small amount of target miss is expected in the treatment using a selected set of the IIFMs. However, additional margin may be necessary to compensate for further motion discrepancies that possibly occur during treatment.

Careful attention should be paid to planning target volume (PTV) margin determination and patient setup when the

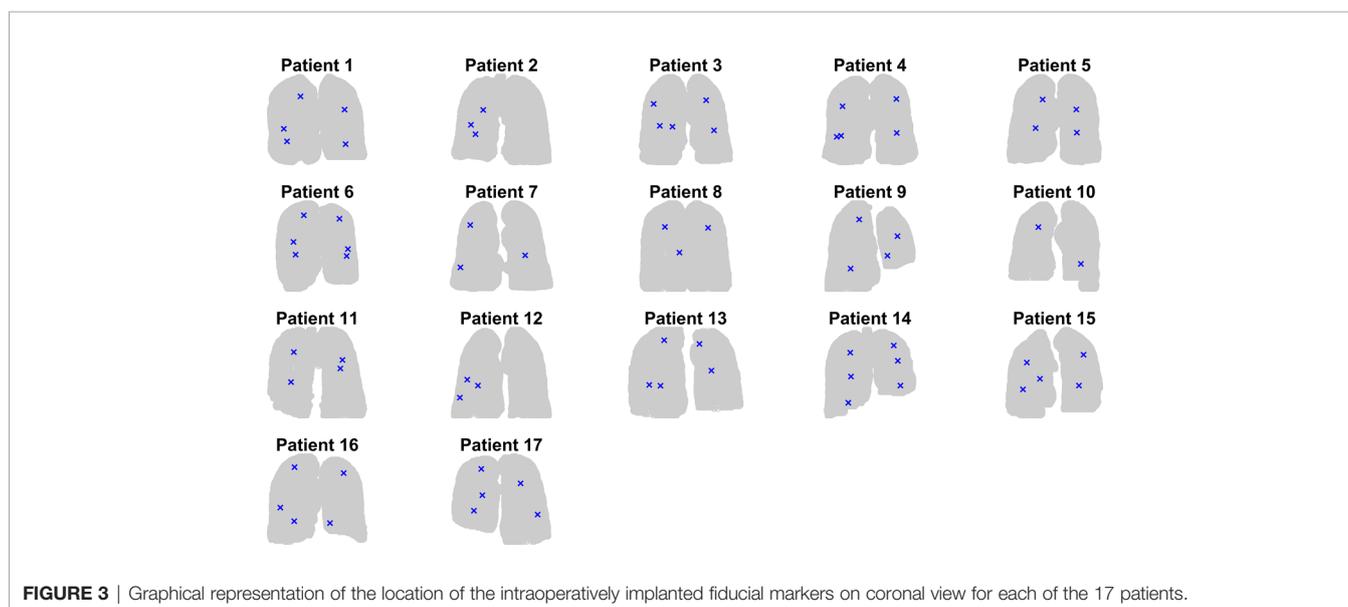
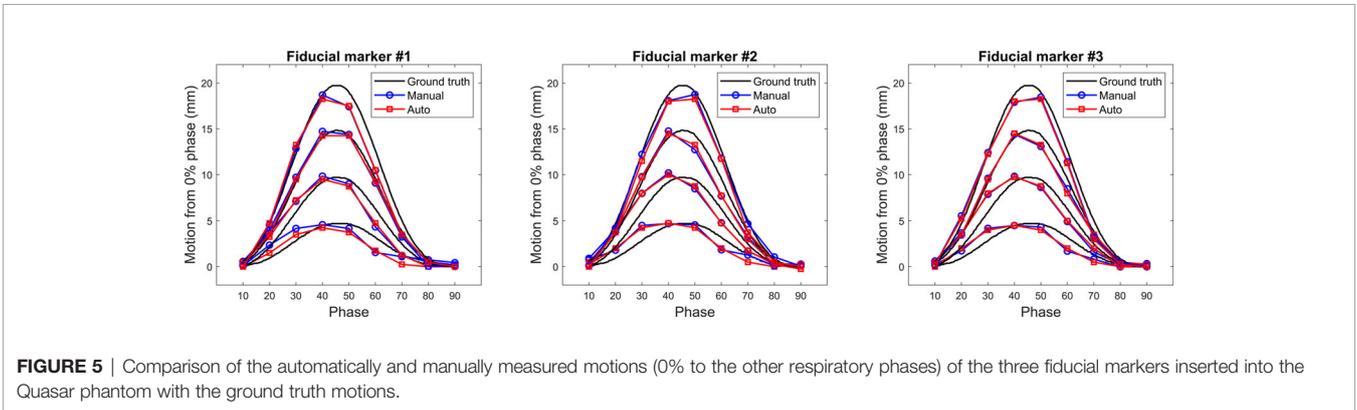
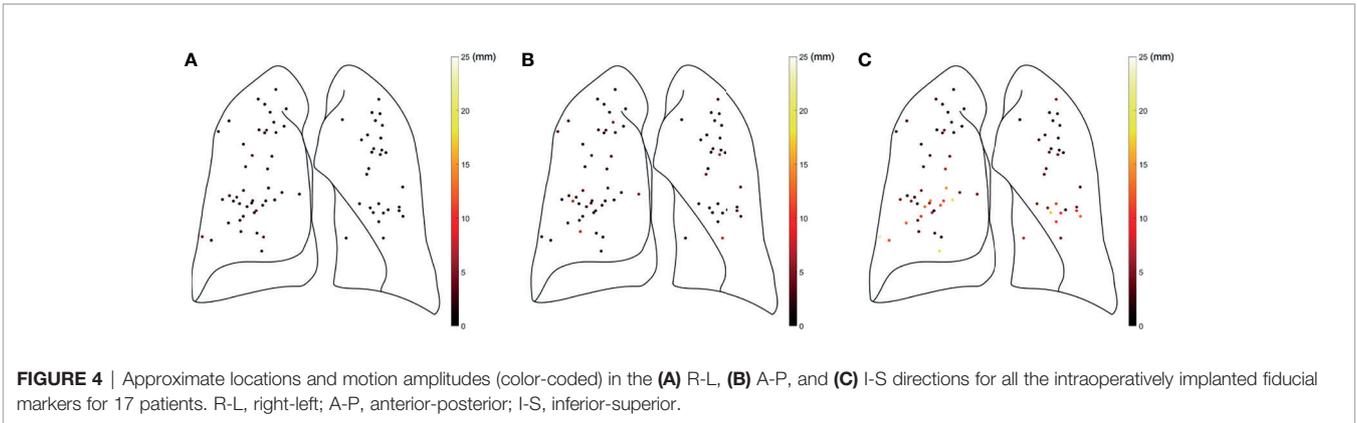
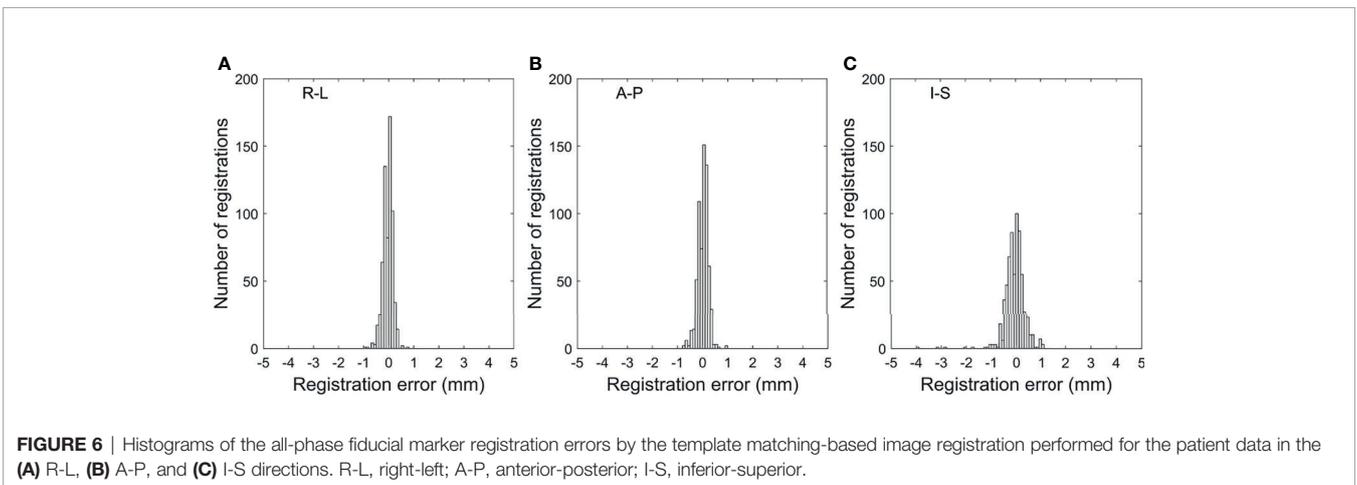


FIGURE 3 | Graphical representation of the location of the intraoperatively implanted fiducial markers on coronal view for each of the 17 patients.



CyberKnife Synchrony tracking is used to treat a lung target with fewer FMs than those recommended by the vendor. In particular, with one FM tracked, a small rotation may result in a large displacement of the lung target from the planned position. Therefore, an appropriate selection of PTV margin and/or accurate patient setup are required for the suggested treatment technique. In this study, when the calculated ITV_{tracking} margin was less than 5 mm, a uniform CTV-to-PTV margin of 5–8 mm was applied. Further investigation is warranted for this purpose.

Furthermore, a dosimetric comparison between the proposed tracking radiation therapy and VMAT plans needs to be performed with careful consideration on PTV margins for both treatment techniques. A CyberKnife Synchrony plan with an appropriate ITV_{tracking} and PTV margins can be dosimetrically advantageous over a VMAT plan when the patient respiratory motion is relatively large, resulting in a larger target volume for VMAT. When CyberKnife Synchrony and VMAT are available for lung SBRT, a decision-making process should be supported



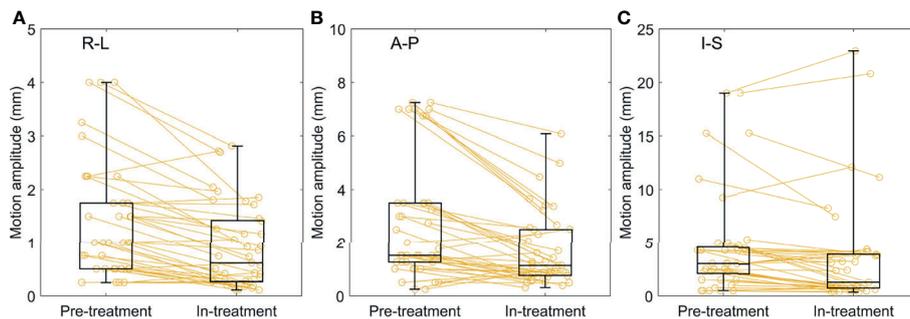


FIGURE 7 | Comparisons of the pretreatment and in-treatment motion amplitudes across 41 treatment fractions of 31 SABR plans in the **(A)** R-L, **(B)** A-P, and **(C)** I-S directions, respectively. The mean values were presented for in-treatment motion amplitudes. SABR, stereotactic ablative radiotherapy; R-L, right-left; A-P, anterior-posterior; I-S, inferior-superior.

by evaluation of dosimetric benefits. Finally, a long-term report on treatment outcomes and toxicity will be required to provide evidence for the proposed treatment approach.

CONCLUSIONS

The feasibility of using the developed margin determination framework for SABR of multiple lung metastases using IIFMs was demonstrated. With careful consideration of accurate patient setup and appropriate selection of PTV margin, the developed margin determination framework can be successfully used to deliver local ablative dose to multiple lung metastases.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Severance Hospital (No. 4-2021-0440, May 26, 2021). Written informed consent for

participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: WK, SP, JC, and C-SH. Methodology: JK, JSK, and C-SH. Software: JK and MH. Validation: JK, MH, and RP. Investigation: KK, HB, and JC. Writing—original draft preparation: JK, JC, and C-SH. Writing—review and editing: JK, JC, C-SH, KK, HB, and SP. Visualization: JK. Supervision: C-SH and SP. All authors contributed to the article and approved the submitted version.

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