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Author(s)	Ueki, Nami; Matsuo, Yukinori; Nakamura, Mitsuhiro; Mukumoto, Nobutaka; Iizuka, Yusuke; Miyabe, Yuki; Sawada, Akira; Mizowaki, Takashi; Kokubo, Masaki; Hiraoka, Masahiro
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1 **Title**

2 Intra- and Interfractional Variations in Geometric Arrangement between Lung Tumours and
3 Implanted Markers

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5

6 **Authors**

7 Nami Ueki, M.D.,¹ Yukinori Matsuo, M.D., Ph.D.,¹ Mitsuhiro Nakamura, Ph.D.,¹ Nobutaka
8 Mukumoto, M.S.,¹ Yusuke Iizuka, M.D.,¹ Yuki Miyabe, M.S.,¹ Akira Sawada, Ph.D.,² Takashi
9 Mizowaki, M.D., Ph.D.,¹ Masaki Kokubo, M.D., Ph.D.,³ and Masahiro Hiraoka, M.D., Ph.D.¹

10

11

12 **Affiliation**

13 ¹ Department of Radiation Oncology and Image-applied Therapy, Kyoto University Graduate
14 School of Medicine, Kyoto, Japan.

15 ² Faculty of medical science, Kyoto College of Medical Science, Nantan, Japan.

16 ³ Department of Radiation Oncology, Kobe City Medical Center General Hospital, Kobe,
17 Japan

18

19

20 **Corresponding author**

21 Yukinori Matsuo, M.D., Ph.D., Department of Radiation Oncology and Image-applied
22 Therapy, Graduate School of Medicine, Kyoto University,

23 Phone: +81-75-751-3762, fax: +81-75-771-9749

24 E-mail: ymatsuo@kuhp.kyoto-u.ac.jp

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28 **Running header**

29 Variation between lung tumour and markers

30

31 **Keywords**

32 Lung cancer, fiducial marker, positional variation, 4DCT.

33

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36 **Abstract**

37 **Purpose:** To quantify the intra- and interfractional variations between lung tumours and
38 implanted markers.

39 **Materials and Methods:** Gold markers were implanted transbronchially around a lung
40 tumour in fifteen patients. They underwent four-dimensional computed tomography scans
41 twice, and the centroids of the tumour and markers were determined. Intrafractional variations
42 were defined as the residual tumour motions relative to the markers due to respiration from
43 the end-exhale phase. Interfractional variations were defined as the residual setup errors after
44 correction for the position of the implanted markers in end-exhale phase images.

45 **Results:** The intrafractional variations differed between patients. The root mean squares of
46 standard deviations for each phase were 0.6, 0.9, and 1.5 mm in the right-left,
47 anterior-posterior, and superior-inferior directions, respectively. The maximum difference in
48 intrafractional variation among 10 phases was correlated with the amplitude of tumour motion
49 in all directions and the tumour-marker distance in the anterior-posterior and superior-inferior
50 directions. The interfractional variations were within 2.5 mm.

51 **Conclusions:** The intrafractional variations differed according to the amount of tumour
52 motion and the tumour-marker distance. Additionally, interfractional variations of up to 2.5
53 mm were observed. Thus, a corresponding margin should be considered during implanted
54 marker-based beam delivery to account for these variations.

55 **Introduction**

56 Stereotactic body radiation therapy (SBRT) is an innovative technique that delivers high-dose
57 radiation limited precisely to the region of the tumour [1,2]. In SBRT for targets affected by
58 respiratory motion, such as lung tumours, appropriate motion management is recommended to
59 reduce doses delivered to the surrounding normal tissues. Several methods of accounting for
60 respiratory motion have been developed, including methods in which the radiation delivery is
61 synchronised with respiration; *i.e.* the dynamic tumour tracking (DTT) method and the
62 respiratory gating method [3].

63 With the above respiratory-synchronised methods, markers implanted either in the
64 tumour itself or nearby are often used as the internal surrogate to localise the tumour position
65 [4-6]. However, the position of the implanted markers does not always represent the tumour
66 position because the tumour and markers move non-synchronously during respiration,
67 especially in cases in which the markers were located slightly distal from the tumour [7]. This
68 intrafractional positional difference between the tumour and markers should be incorporated
69 into the DTT or respiratory gating irradiation treatment plan by using a wider gating window,
70 within which the beam is delivered during the respiration cycle. Furthermore, the relative
71 position of the tumour with respect to the markers may vary from day to day; therefore, the
72 interfractional positional difference must be addressed. However, little about these variations
73 is known.

74 The purpose of this study was to quantify the intra- and interfractional variations
75 between the lung tumour position and the position of the implanted markers to evaluate the
76 margin necessary to account for the associated errors during respiratory-synchronised
77 irradiation treatment.

78

79 **Materials and Methods**

80 *Patients and implanted markers*

81 Fifteen patients who underwent SBRT for a solitary lung tumour were enrolled in this study.
82 With the approval of the Institutional Review Board, written informed consent was obtained
83 from all patients. One to two weeks prior to the date of the computed tomography (CT)
84 simulation, four or five disposable gold markers (Olympus Corporation, Tokyo, Japan),
85 spherical markers with a diameter of 1.5 mm, were implanted transbronchially. The insertion
86 technique was similar to the one reported by Harada *et al* [4]. Prior to the implantation, the
87 relative position between tumour and bronchi was evaluated on the multiplanar reformatted
88 CT images. The markers were implanted into the peripheral surrounding bronchi near tumour
89 under fluoroscopy guidance. A total of 66 markers were placed. The median interval between
90 marker placement and the CT simulation was 8 (range, 2 to 16) days. Twelve markers were
91 coughed up before CT simulation. After CT simulation, 2 markers were coughed up on the
92 seventh and thirteenth day, and 1 marker migrated on the sixth day after insertion. The
93 markers that coughed up or migrated after CT simulation during the treatment period were
94 excluded from this analysis. No adverse effect associated with the implantation was observed.
95 The characteristics of patients and tumours are shown in Table 1.

96

97 *Patient set-up and four-dimensional CT data acquisition*

98 The patients were immobilised using vacuum immobilisation devices: BodyFix system
99 (Elekta AB, Stockholm, Sweden) or Esform (Engineering System, Nagano, Japan). After
100 set-up with skin marks, four-dimensional CT (4DCT) data were acquired using a
101 16-multidetector row CT: LightSpeed RT or BrightSpeed (General Electric Healthcare,
102 Waukesha, WI, USA) with an axial slice thickness of 2.5 mm. The cine duration time of the
103 scan at each couch position was set to 6.0 or 7.0 s, which was more than the maximum

104 observed respiratory period. Simultaneously, the respiratory phase was monitored using the
 105 Varian Real-time Position Management system (Varian Medical Systems, Palo Alto, CA,
 106 USA) under free breathing without coaching. CT slices and respiratory phase data were
 107 transferred to the Advantage SIM workstation (General Electric Healthcare, Waukesha, WI,
 108 USA) and sorted into 10 respiratory phase bins. Motion phases were assigned for each
 109 respiratory phase as percentages; end-inhalation corresponded to 0% and end-exhalation to
 110 50%. 4DCT scans were performed during the CT simulation (CT-1) and repeated once during
 111 the course of treatment (CT-2). Fifteen pairs, corresponding to a total of thirty 4DCT scans,
 112 were obtained. The median period from the day of CT-1 until the day of CT-2 was 8 days
 113 (range, 4 to 12). All 4DCT datasets were imported into a commercial radiotherapy planning
 114 system, iPlan 4.5.1 (BrainLAB AG, Fieldkirchen, Germany).

115

116 *Analysis*

117 The intrafractional variations assessed in this study were defined as the residual tumour
 118 motions relative to the markers due to respiration. In all 10 phases of the CT-1 scans, gross
 119 tumours and implanted markers were contoured manually with a pulmonary window setting
 120 (window level, -700 Hounsfield units; window width, 2000 Hounsfield units) by a single
 121 radiation oncologist. The centroid of the tumour $G_{t,n} = (x_{t,n}, y_{t,n}, z_{t,n})$ and the centroids of all 3
 122 to 5 markers $G_{m,n} = (x_{m,n}, y_{m,n}, z_{m,n})$ were recorded at $n\%$ respiratory phase ($0 \leq n \leq 90$). The
 123 coordinates (x, y, z) correspond to the right-left (RL), anterior-posterior (AP), and
 124 superior-inferior (SI) directions, respectively. Along each axis, a positive value corresponds to
 125 the right, anterior, and superior directions. The relative position of the tumour and centroid of
 126 markers for each phase was represented by the vector $V_n = G_{t,n} - G_{m,n}$. Using the relative
 127 positions on 50% phase images (V_{50}) as a reference, the error $E_n = V_n - V_{50}$ was calculated.
 128 The mean (M_n) and standard deviation (SD_n) of E_n in fifteen 4DCT CT-1 datasets were also

129 calculated. The mean and SD of M_n ($0 \leq n \leq 90$) were calculated to evaluate systematic
130 displacement between respiratory phases. The root mean square (RMS) of SD_n ($0 \leq n \leq 90$) was
131 calculated to evaluate interpatient variations. The range of intrafractional variations is defined
132 as the maximum difference in E_n among 10 phases for each direction. To evaluate the
133 influence of the tumour motion amplitude and the tumour-marker distance on the ranges of
134 intrafractional variations, a multiple linear regression analysis was performed. The tumour
135 motion amplitude was defined as the maximal difference in the tumour centroid position
136 among the 10 respiratory phases in each direction. The tumour-marker distance in each
137 direction was defined as the distance between the tumour centroid and the centroid of all 3 to
138 5 markers in the 50% phase images.

139 The interfractional variations in this study represent the residual setup errors after
140 correction based on the implanted markers. Firstly, to correct the rotational set up errors, the
141 50% phase images for CT-2 were rigidly registered to the 50% phase images of CT-1 based on
142 bony structure. Then the translational errors were modified by registering those images based
143 on the marker centroids. The interfractional variations were evaluated as the residual
144 difference in the tumour centroids for each direction between CT-1 and CT-2 for each patient.

145

146 **Results**

147 *Tumour motion amplitude and tumour-marker distance*

148 The median (range) tumour motion amplitudes in CT-1 were 1.8 mm (0.4 to 5.6), 3.1 mm (0.6
149 to 7.8), and 8.2 mm (0.9 to 28.9) in the RL, AP, and SI directions, respectively. The median
150 values (range) of the distance between the tumour centroid and the centroid of all markers in
151 the 50% phase images for CT-1 were 11.9 mm (1.9 to 30.5), 8.1 mm (0.7 to 35.3), and 10.3
152 mm (0.3 to 30.1) in the RL, AP, and SI directions, respectively.

153

154 *Intrafractional variations*

155 The divergence in the range of intrafractional variations between patients is shown in Fig. 1,
156 and the values of E_n in the respiratory phases ($0 \leq n \leq 90$) are shown in Fig. 2. The means \pm SD
157 of M_n ($0 \leq n \leq 90$) were 0.1 ± 0.1 mm, 0.3 ± 0.2 mm, and 0.0 ± 0.2 mm, and the RMS of SD_n were
158 0.6 mm, 0.9 mm, and 1.5 mm in the RL, AP, and SI directions, respectively. These results
159 indicate that the systematic difference between respiratory phases is negligible. In addition, as
160 shown in Fig. 2, the further towards inhale then the greater the intrafractional variations.

161 The tumour motion amplitude was positively correlated with the range of
162 intrafractional variations in all directions, and the tumour-marker distances were also
163 positively correlated in the AP and SI directions (Table 2).

164

165 *Interfractional variations*

166 The median (range) interfractional variations were -0.1 mm (-2.4 to 0.7), 0.1 mm (-2.3 to 2.4),
167 and -0.6 mm (-1.3 to 1.6) in the RL, AP, and SI directions, respectively. As shown in Fig. 3,
168 all interfractional variations were within 2.5 mm; the greatest variations were in the AP
169 direction. The 95th percentiles of interfractional variations for one side of each direction were
170 0.6 and 2.1 mm to the right and left, 1.9 and 2.1 mm in the anterior and posterior directions,
171 and 1.6 and 1.3 mm in the superior and inferior directions.

172

173 **Discussion**

174 Implanted markers are often used as a surrogate for the tumour position in radiation therapy
175 for lung tumours. The transcutaneous and transbronchial approaches are the two major
176 methods for implantation of markers in the vicinity of lung tumours [8-13]. These procedures
177 may cause pneumothorax as a complication, which can delay radiation delivery and could be
178 life-threatening for those with comorbidities. The incidences of all pneumothorax and of those

179 requiring chest tube placement after transcutaneous implantation have been reported to be 30
180 to 67% and 16 to 40%, respectively [8-10]. By contrast, the reported incidence of
181 pneumothorax with the transbronchial approach is low [10-13] and in our series no
182 complication was observed. Therefore, the transbronchial approach is preferable due to its
183 less invasive nature. However, the placement of markers near or inside the tumour is more
184 difficult with the transbronchial approach than with the transcutaneous approach, because in
185 the former the markers are placed along the small bronchi near a tumour. The greater distance
186 between the tumour and markers leads to a larger positional error [14]. This error must be
187 considered when performing radiotherapy using markers placed outside the tumour. In the
188 current study, we quantified the intra- and interfractional positional variations between the
189 lung tumour and implanted markers using 4DCT scans to determine the necessary margin for
190 respiratory-synchronised irradiation using implanted markers. Another issue about the
191 markers implanted transbronchially is the low fixation rate. In our series, the fixation rate of
192 implanted markers was 77.3%: 51 of 66 markers implanted markers were fixed throughout
193 treatment. This is comparable to the reported fixation rate using the same insertion technique
194 [11]. Due to the low fixation rate, we inserted 4 or 5 markers to avoid an additional insertion
195 procedure and used multiple markers as a surrogate for the tumour position to address the
196 change in geometric arrangement of markers by dislocation.

197 Although several authors reported the intrafractional verification of the tumour position
198 by the kilo-voltage (kV) X-ray images during gating irradiation, they calculated the tumour
199 positions from the detected positions of the implanted markers assuming the relative position
200 between the tumour and markers were constant [7,15]. The planar kV X-ray imaging is
201 superior to CT in terms of the temporal resolution but it is difficult to quantify the motion of
202 tumor itself accurately on the projected images. To quantify the variations between the tumour
203 and implanted markers, we used 4DCT. Two studies are available which evaluated the

204 geometrical difference between tumour and markers due to respiration using 4DCT. Smith *et*
205 *al.* analysed the motion of lung tissue in 10 patients with deformable registration between
206 exhalation and inhalation of 4DCT scans and reported stronger correlations between tumour
207 and surrounding lung tissues in the upper lobes than in the lower lobes [16]. Finally, they
208 concluded that the correlation between the tumour and the surrounding tissue was highly
209 specific to the patient and lobe [16]. Since the amplitude of the tumour motion is typically
210 smaller in the upper lobe than that in the lower lobe, then it is likely the bigger variations
211 observed in lower lobe tumours by Smith *et al.* may be related to the amplitude of motion.
212 Yamazaki *et al.* evaluated the distances between tumours and the distal bronchi during
213 respiration cycle with 4DCT for 8 patients. They showed that the distances in the mid-inhale
214 to end-inhale phase images were significantly larger than the distances in the end-exhale
215 phase images [17]. Smith *et al.* and Yamazaki *et al.* suggested that markers that are closer to
216 the tumour give a more accurate representation of tumour motion [16,17]. These results are
217 consistent with our findings: the values needed to compensate for the intrafractional variations
218 differed between patients, and depended on the amplitude of tumour motion and the
219 tumour-marker distance.

220 Moreover, our results indicated that the intrafractional errors were different for each
221 patient both in direction and in amplitude, as shown in Fig 1. A uniform isotropic margin was
222 not adequate to cover the errors observed. Consequently, the variations must be evaluated on a
223 per-patient basis and compensated for by addition of a patient-specific margin in DTT or
224 gating irradiation treatment with a wider gating window. In our treatment planning process of
225 DTT, we create an enlarged target volume which cover the intrafractional variations in the
226 following steps. Firstly, 4DCT images from each phase are translated based on the centroid of
227 the markers. Then, the phase images are superimposed onto the 50% phase image that is used
228 as a reference image set. Finally, the enlarged target volume is delineated encompassing gross

229 tumour volumes on all fused phase image. This enlarged volume can compensate for the
230 patient-specific intrafractional variations.

231 All interfractional variations in the present study were within 2.5 mm. Previous reports
232 on interfractional variations between lung tumours and implanted markers are summarised in
233 Supplementary Table 1 (Electronic Appendix). The reported values are larger than those in
234 this study. This discrepancy may be attributed to two causes. One is a change in
235 tumour-marker distance during the course of treatment. Several investigators reported tumour
236 shrinkage and deformation after radiotherapy with conventional fractionation [5,10,14], which
237 altered the distance. Meanwhile, Imura *et al.* [11] evaluated the interfractional variations in
238 the distances between markers using orthogonal X-ray images with a median treatment time
239 of 6 days, and showed that the variations during treatment were within 2 mm in 95% of cases.
240 Their results support our finding that the interfractional variation between the tumour and
241 markers was smaller in those undergoing hypofractionated treatment than in those undergoing
242 conventional fractionation. A second interesting finding was the respiratory phase
243 reproducibility. Van der Voort van Zyp *et al.* assessed marker displacement compared to the
244 centroid of the tumour in patients that underwent SBRT; however, their results were
245 influenced by the nonsynchronous tumour-marker motion due to divergence in the timing of
246 breath holding [6]. Persson *et al.* also used the breath-hold CT with voluntary deep inspiration
247 [18]. The interfractional variations in the current study were evaluated using end-exhale phase
248 images under free breathing, which has high reproducibility compared with breath-holding.

249 Several limitations of our study should be mentioned. Firstly, the intrafractional
250 variations evaluated with 4DCT during a few respiration cycles may not be representative of
251 those during treatment in some patients although a single 4DCT is thought to be reliable for
252 the tumour motion in the majority of patients [19]. Therefore, in our institution, we validate
253 margins to compensate for the intrafractional variations, by visual verification with kV x-ray

254 fluoroscopy after the margins are determined based on the simulation 4DCT. Secondly,
255 motion artefacts affected the contouring of tumours and implanted markers evaluated in
256 binned 4DCT images. Because of this uncertainty in contouring, the intrafractional variations
257 for tumours with larger motion may be over- or underestimated [20]. Furthermore, we
258 evaluated the position of markers of 1.5-mm diameter using 4DCT with a 2.5-mm axial slice
259 thickness. The use of 2.5-mm CT slice thickness would affect the accuracy of contouring the
260 markers, with a maximum uncertainty of localising tumours and markers of 1.25 mm in the SI
261 direction [6]. Those errors could be reduced by acquiring CT images with a thinner axial slice
262 thickness or by the volumetric acquisition [21,22].

263

264

265 **Conclusions**

266 Intrafractional variations of the difference between tumour centroid and marker centroid
267 position increased with both tumour motion amplitude and tumour-marker distance.
268 Additionally interfractional variations of the distance between between tumour centroid and
269 marker centroid position were observed up to 2.5mm. Thus, an appropriate margin to account
270 for these variations should be considered when planning implanted-marker-based beam
271 delivery.

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335

336

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341

342 **Conflicts of interest**

343 Takashi Mizowaki, Masaki Kokubo, and Masahiro Hiraoka have a consultancy agreement
344 with Mitsubishi Heavy Industries, Ltd., Japan.

Figure legends

Fig. 1. The range of intrafractional variations in the RL (a), AP (b), and SI (c) directions for each patient rearranged according to the three-dimensional tumour motion amplitude in descending order. *Abbreviations:* RL, right-left; AP, anterior-posterior; SI, superior-inferior

Fig. 2. E_n values in the RL (a), AP (b), and SI (c) directions for each respiratory phase. E_n is the error in the relative position of the tumour to the centroid of the markers on $n\%$ phase images ($0 \leq n \leq 90$), using the relative position on the 50% phase images as a reference. Other abbreviations are as in Fig. 1.

Fig. 3. Interfractional variation in the RL, AP, and SI directions. Abbreviations are as in Fig.

1.

Table 1. Characteristics of patients and tumours (n=15).

Characteristics	$n = 15$
Age (y)	
Median	82
[range]	[54–87]
Gender	
Male	12
Female	3
Tumour size	
≤ 20 mm	4
>20 to ≤ 30 mm	6
>30 to ≤ 50 mm	5
Tumour location	
Right middle lobe	2
Right lower lobe	7
Left upper lobe	2
Left lower lobe	4
No. of implanted markers	
4	9

5	6
<hr/>	
No. of markers evaluated	
3	10
4	4
5	1
<hr/>	

Table 2. Predictive factors for the range of intrafractional variation as determined by multiple linear regression analysis.

Predictive factor	Range of intrafractional variation					
	RL		AP		SI	
	β	p	β	p	β	p
Tumour motion amplitude	0.539	0.048	0.428	0.076	0.591	0.011
Tumour–marker distance	-0.051	0.84	0.449	0.064	0.327	0.012
R	0.549		0.649		0.780	

Abbreviations: R, correlation coefficient; other abbreviations are as in Fig. 1.

Supplementary Table 1. Summary of reports of interfractional variation between tumours and markers.

Author	n	Modality	Implanted Markers			Result
			n	Shape	Insertion	
Nelson <i>et al.</i> [5]	5	4DCT	1 to 4	Cylinder	Transbronchial	6 ± 3 mm*
Roman <i>et al.</i> [14]	7	4D CBCT	2 to 4	Long coil	Transbronchial	4 ± 2 mm (lateral), 3 ± 2 mm (AP), and 4 ± 3 mm (SI) *
Kupelian <i>et al.</i> [10]	23	Breath-hold CT (exhale)	NA	Long coil	Transcutaneous / Transbronchial	2.6 ± 1.3 mm* (range, 0.2 to 5.4)
Van der Voort van Zyp <i>et al.</i> [6]	42	Breath-hold CT (exhale)	3	Cylinder	Transcutaneous	Median 1.3 mm (range, 0.1 to 53.6)
Persson <i>et al.</i> [18]	14	Breath-hold CT (inhale)	1	Long coil	Transcutaneous	Range: -2.9 to 2.6 mm (LR), -1.8 to 1.5 mm (AP), and -2.6 to 2.8 mm (SI)
This study	15	4DCT (50%)	3 to 5	Sphere	Transbronchial	All values in each direction were within 2.5 mm

* mean ± standard deviation.

Abbreviations: 4D, four-dimensional; CT, computed tomography; CBCT, cone-beam CT; RL, right-left; AP, anterior-posterior; SI, superior-inferior

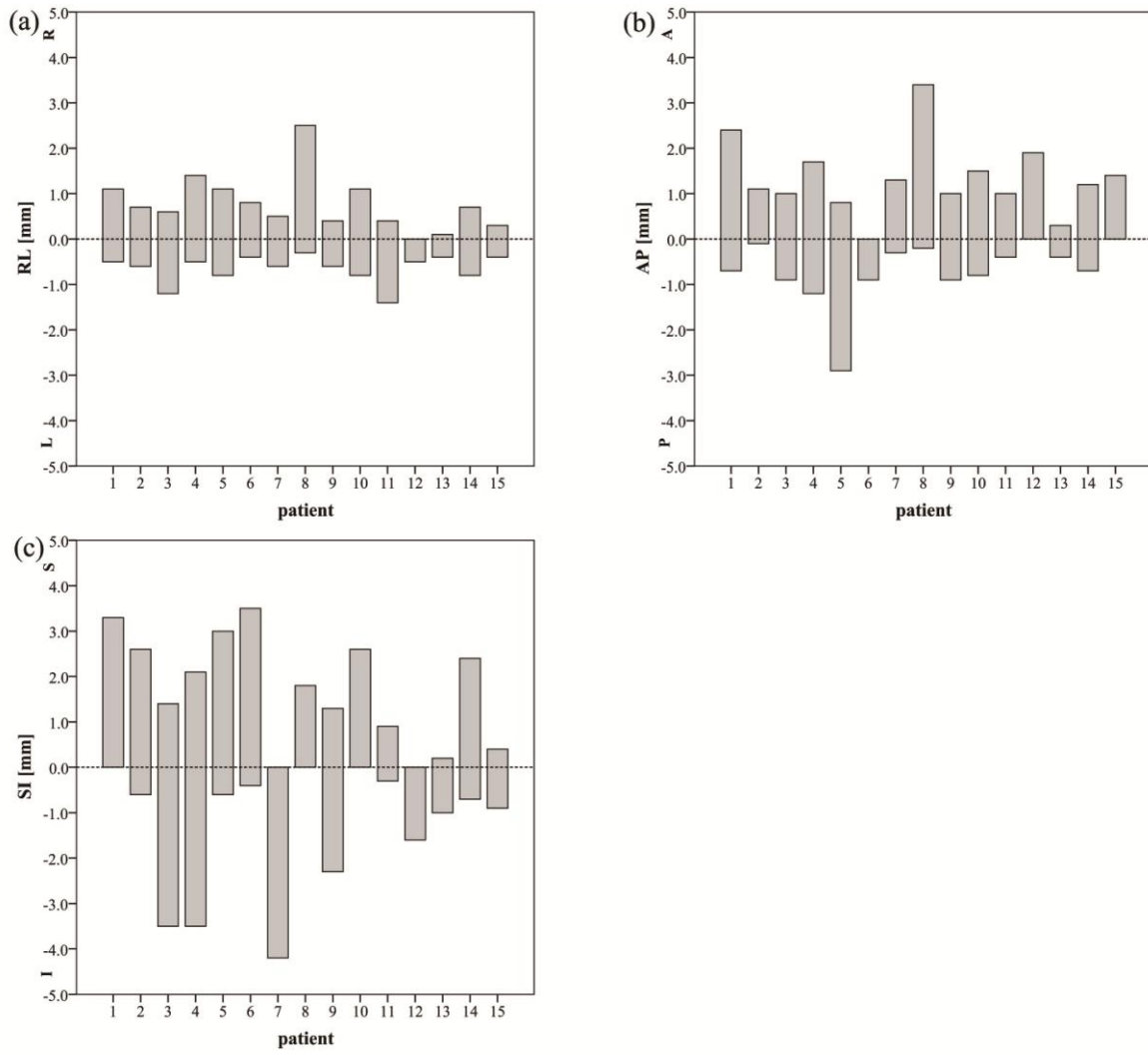


Fig. 1.

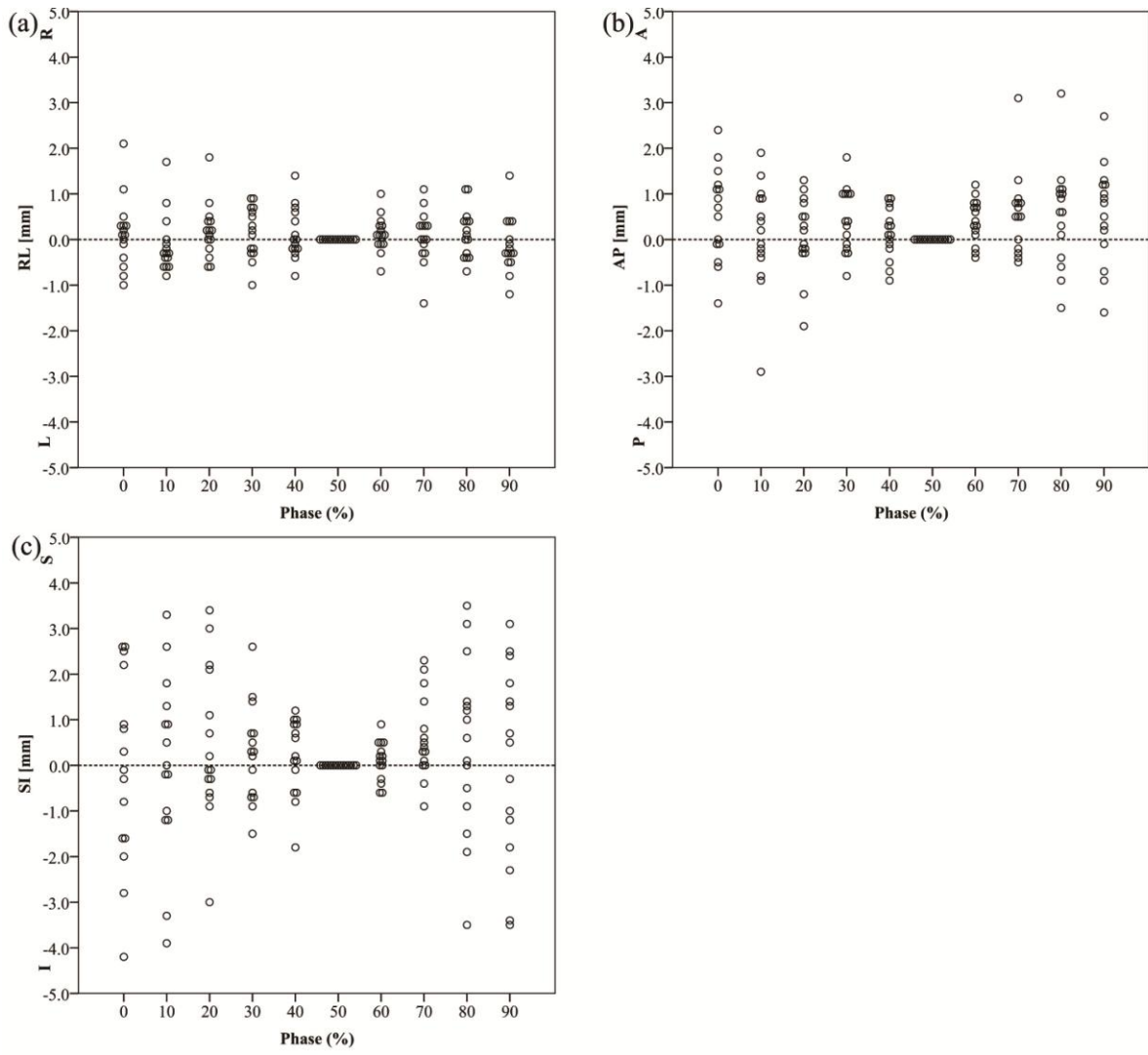


Fig. 2.

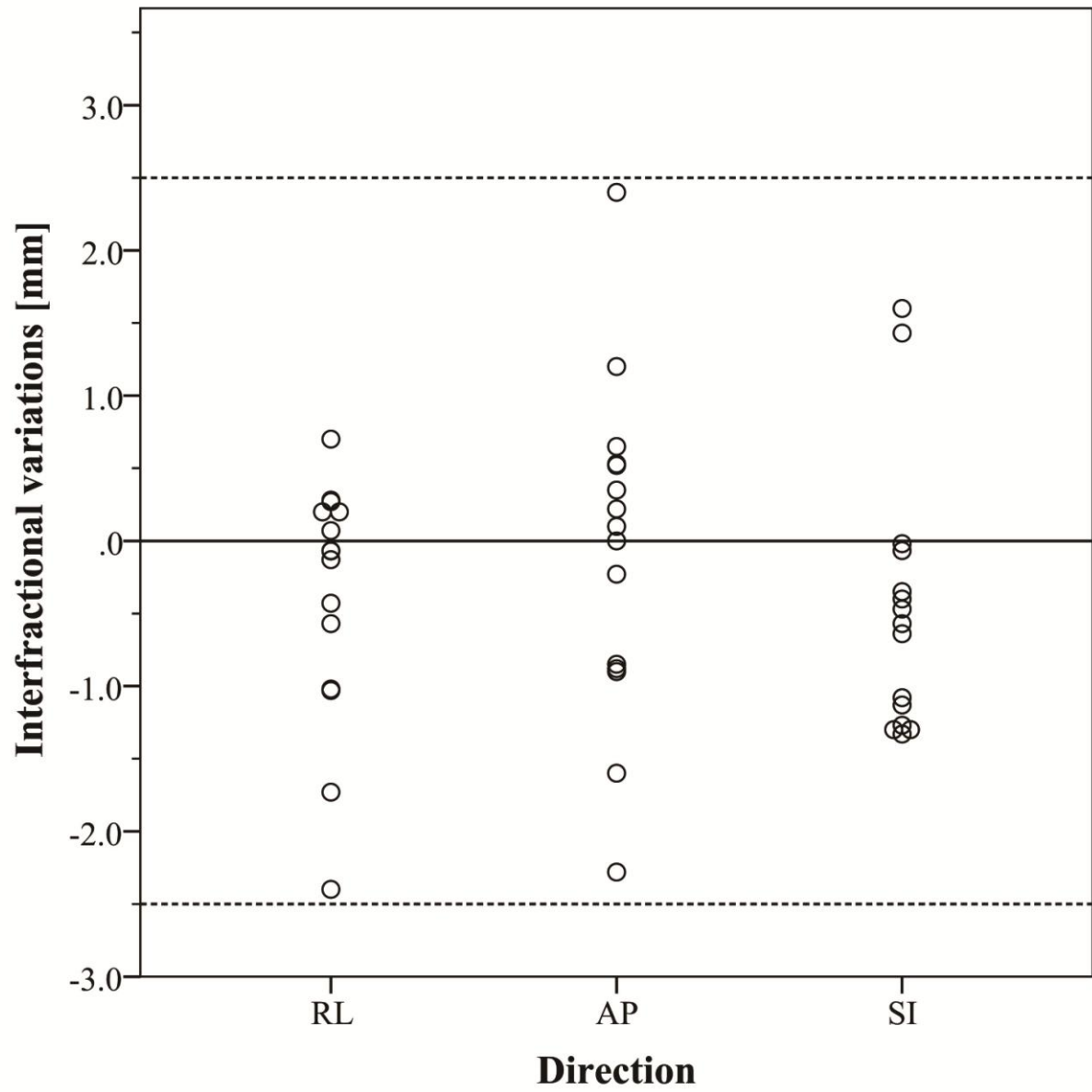


Fig. 3.