Journal name: Radiological Physics and Technology
Article type: Technical Notes

Title: Influence of respiration on dose calculation in stereotactic body radiotherapy of the lung

Authors: Rie Yamazaki[1], Rikiya Onimaru[2], Norio Katoh[2], Tetsuya Inoue[2], Takeshi Nishioka[3], Hiroki Shirato[2], and Hiroyuki Date[3]

Affiliation and addresses:
[1]Graduate School of Health Sciences, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo, 060-0812, Japan
[2]Department of Radiation Medicine, Hokkaido University School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo, 060-8638, Japan
[3]Faculty of Health Sciences, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo, 060-0812, Japan

Corresponding author: Hiroyuki Date
Affiliation: Faculty of Health Sciences, Hokkaido University
Postal address: Kita-12, Nishi-5, Kita-ku, Sapporo, 060-0812, Japan
Telephone: 011-706-3423 / Fax: 011-706-4916
E-mail: date@hs.hokudai.ac.jp

Conflict of interest: No actual or potential conflicts of interest exist for all authors.

The manuscript has not been published previously nor concurrently submitted for publication elsewhere.

Abstract

Our purpose in this study was to evaluate the variation of calculated doses caused by respiration in stereotactic body radiotherapy (SBRT) of the lung. The study targeted 10 patients who underwent SBRT for lung tumors. CT images were acquired during free breathing, and in the inhalation and exhalation phases. We compared the CT image at inhalation with the image at exhalation so as to measure the change in lung volume, variation of the CT value, and displacement of the chest wall. The lung volume change was shown to be correlated with the maximum of the chest wall motion and with the variation in the CT value. A statistically significant difference was observed in the CT values between inhalation and exhalation ($p<0.05$). The total dose variation at the isocenter was confined within ±2%. However, the dose from individual beams can vary significantly when the chest wall moves more than 10 mm in natural breathing.

Keywords

stereotactic body radiotherapy, lung tumor, respiration, dose calculation, chest wall motion

1. Introduction

Stereotactic body radiotherapy (SBRT) for isolated tumors has been widely used in recent years because it provides good local control and a survival rate comparable to that for surgery [1, 2]. In radiotherapy of lung cancers, the respiratory motion of the tumors causes a large uncertainty. Therefore, the influence of respiration on the dose delivery and a sufficient margin around the tumor must be considered in SBRT for lung tumors [3]. The internal target volume can be determined, for example, via monitoring with four-dimensional computed tomography (4DCT), or with the acquisition of CT imaging times both at inhalation and exhalation. For sparing of normal tissue, there are various techniques such as the use of a body frame, breath holding, infra-red light monitoring of the chest wall, and real-time tumor tracking with implanting of fiducial markers [3-7]. However, unfavorable outcomes, such as inconsistent breathing, discrepancies between chest wall motion and tumor motion, and misalignments between the tumor and an implanted fiducial marker have been reported with these techniques [3, 8, 9].

Furthermore, the treatment dose may be affected by the fact that the lung includes a large portion of low density regions. Chang *et al*. reported that variations in tissue densities are not significant in many sites outside the thorax, and that lung tissue typically has a physical density of approximately 30% that of soft tissue [10]. Recent calculation algorithms (e.g., the Monte Carlo method) provide more precise dose calculations [11], suggesting that a slight change in density may significantly influence the dose distribution. Therefore, a three-dimensional heterogeneous correction is necessary in dose calculations for the lung [12, 13].

Our purpose in this study was to evaluate the variation in the calculated dose due to

respiration in SBRT of the lung. We showed that the dose calculation is influenced by the change in lung volume, the variation of the CT value of the lung, and the movement of the chest wall due to the respiration. We evaluated the variation in the dose by using CT images of the lung with tumors at the inhalation and exhalation phases.

2. Materials and Methods

2.1 Patient characteristics and irradiation regimens

The study targeted 10 patients with lung cancer who underwent SBRT from September 2012 to April 2013. This study was approved by the ethics committee of the Hokkaido University Hospital. For each patient, CT images during free breathing, and at the inhalation and exhalation phases, were acquired (GE Healthcare, Optima CT580W, operated at 120 kV) with 2.5 mm-slice thickness. We gave sufficient explanation to the patients for performing natural inhalation and exhalation breath holding. The median patient age was 77 years (range: 55-89 years), and the male/female ratio was 4:1. The tumors were located in the upper lobe (n=8) and lower lobe (n=2). Irradiation regimens were 40 Gy in four fractions to the 95% volume of the planning target volume (PTV) (n=5), 48 Gy in four fractions at the isocenter (n=2), and 48 Gy in eight fractions at the isocenter (n=3). CT images with free breathing were used for treatment planning with six X-ray beams. All cases were planned for a 6 MV photon beam irradiation. The gross tumor volume (GTV) was first defined as the visible tumor on the CT images under free breathing. Then, the internal target volume (ITV) was determined by superimposition of the GTVs based on the CT images at the inhalation and exhalation phases. The clinical target volume (CTV) was obtained as the GTV plus ITV, and the PTV was configured as the CTV plus a 5-mm margin. Before the treatment,

we used an image guided system (OBI: on board imaging, Varian Medical Systems).

2.2 Measurements of lung volume and chest wall motion

The lung was delineated manually, and the volume of each lung was measured by a volume rendering software in the CT workstation (GE Healthcare, Advantage SIM). Then, the inhalation/exhalation (I/E) ratio of the lung volume was calculated. In this study, the chest wall motion was defined as the variation in the distance of the chest wall surface from the midline of the body.

2.3 Lung density analysis

During the periods of inhalation and exhalation, CT values were measured at three locations (anterior, exterior, and posterior) in three slices (at the tracheal bifurcation, at the intermediate between the tracheal bifurcation and the lung apex, at the intermediate between the tracheal bifurcation and the lung base), by use of the CT workstation (GE healthcare, Advantage SIM). The area of the region of interest (ROI) was 2 cm^2. The ROI area was configured to represent three locations, avoiding the large vessels. Example ROIs are shown in Fig.1.

2.4 Dose calculation

The dose calculation by use of a superposition algorithm was performed with a radiation treatment planning system (Elekta, XiO, ver. 4.70). The beam arrangements (e.g., field size, isocenter, gantry angle, and irradiation monitor unit) were the same as those of treatment-planning with free-breathing CT images. In this study, we did not consider the variation of the clinical target volume arising from breathing motion. The

total dose and the dose of each field (i.e., six beams in this planning) at the isocenter were obtained. Patients actually received the free-breathing treatment. We compared the calculated doses at inhalation and exhalation with those of the free-breathing. The variation of the dose was evaluated by a difference from the calculated dose in free breathing as a reference. The volumes of the lung receiving 20 Gy (V20) and receiving 5 Gy (V5) were also measured at inhalation and at exhalation.

2.5 Statistical analysis

For statistical analysis, JMP Pro v10 (SAS Institute, Cary, North Carolina, USA) was used. The variation of the mean CT values and the calculated doses in free breathing as a reference were observed at inhalation and exhalation. The differences in these quantities between inhalation and exhalation were analyzed with a paired t-test, which was considered to be statistically significant when $p<0.05$.

3. Results

3.1 Variations of the lung volume and the CT value with respiration

In this study of 10 patients, the median I/E ratio of the lung volume was 1.28 (range: 1.03-1.65). CT values ranged from -917 HU to -475 HU. Figure 2 shows the relationship between the lung volume I/E ratio and the maximum motion of the chest wall, and the relationship between the lung volume I/E ratio and the variation in the CT value. As the lung volume I/E ratio increases, the maximum of the chest wall motion and the variation of the CT value have tendencies to become larger. The coefficient of correlation for the maximum of the chest wall motion was $r=0.82$, and for the variation of the CT value, $r=0.78$. Figure 3 shows the variation of the CT value during respiration

(e.g., from inhalation to exhalation). Eighteen ROIs were measured for each patient. The CT value of each ROI was obtained by averaging of those of the right lung and left lung on the same slice. A statistically significant difference in the variation of the mean CT values between inhalation and exhalation was observed in all ROIs ($p<0.05$, paired t-test).

3.2 Dose calculation

The total dose difference at the isocenter with respect to the lung volume I/E ratio is shown in Fig.4. All points are within ±2%, regardless of inhalation or exhalation. Figure 5 shows the dose difference of each field versus the maximum of the motion of the chest wall. A statistically significant difference in the dose variation between inhalation and exhalation was observed ($p<0.05$, paired t-test). If the maximum displacement data of the chest wall are divided into two groups, below 10 mm (n=6) and above 10 mm (n=4), the dose difference between inhalation and exhalation is larger for the latter group ($p<0.05$, paired t-test). Figure 6 shows the difference of V20 (exhalation minus inhalation (E-I)) and the difference of V5 (E-I) with respect to the lung volume I/E ratio. The difference of V20 (E-I) and the difference of V5 (E-I) are likely to be larger with increasing lung volume I/E ratio. The coefficient of correlation for the V20 (E-I) difference is r=0.80, and for V5 (E-I) it is r=0.84.

4. Discussion

In this study, the variation of the lung volume, CT value, and chest wall in respiration were investigated. The variation of the lung volume was shown to be correlated with the maximum of the chest wall motion and also with the variation of the

CT value. However, the influence of respiration on the dose calculation was confined within ±2%.

Aarup *et al.* [12] reported that the lung density is variable from 0.4 to 0.1 g/cm^3 during the treatment period between the expiration phase of breathing (or in free breathing with a mean lung density similar to that of expiration) and deep inspiration breath-hold. Our study showed that the lung density ranges from 0.5 g/cm^3 to 0.1 g/cm^3 according to a conversion table registered with the treatment planning system.

The maximum of the chest wall motion ranged from 0.5 mm to 21.0 mm. Although the manner of breathing includes thoracic respiration and abdominal respiration, these were not considered in our study. Plathow *et al.* [14] reported on the influence of different breathing techniques (i.e., abdominal breathing, thoracic breathing, and natural breathing) on internal and external organ motions by using dynamic MRI with fiducial markers. They showed that there is no significant difference among the three breathing techniques for quiet breathing. It was also shown that the maximum antero-posterior distances of the lung in normal breathing at inspiration are 11.6 ± 1.1 cm and at expiration, 9.8 ± 0.8 cm. Their results are in fairly good agreement with ours.

The total dose variation at the isocenter was within ±2% between inhalation and exhalation in our study. Mexner *et al.* [15] reported that relative differences in the minimum gross tumor volume dose were less than 2% for all patients, and that the overall effect accumulated over the respiratory cycle was very small. We evaluated the point dose at the isocenter, which provides a result similar to theirs. However, it should be noted that the dose may vary significantly when the chest wall motion is more than 10 mm.

Radiation pneumonitis has been a major problem following SBRT [16-18]. The

dose-volume histogram (DVH) is widely used for assessment of the risk of the pneumonitis. We evaluated the difference in V20 and the difference in V5 between inhalation and exhalation. Mexner *et al.* [15] reported that the relative difference is not more than 1% for V20. Our study also indicates that the mean of the difference of V20 is 0.9% (ranging from -0.3% to 3.9%) and that of V5 is 1.8% (ranging from -2.5% to 5.1%). V20 and V5 are correlated with the lung volume change.

In general, the variation of the total dose was observed to be small in our study. This may be because most tumors were located in the upper lobe. Tumors located in the lower lobe may lead to different results. Although the use of 4DCT might be of help for performing dynamic dose calculations [19, 20], in our experience 4DCT data acquisition is difficult unless breathing is performed regularly with a large amplitude.

5. Conclusion

In this study, the variation in the dose estimation during natural respiration was evaluated. The results show that tumors located in the upper lobe affect the dose calculation slightly in the respiration period, and the total dose variation at the isocenter is within ±2%. However, it was observed that respiration influences the dose calculation when the chest wall motion is large (above 10 mm) in natural breathing. This study shows that the maximum dose difference between inhalation and exhalation was within ±2%. In other words, it was suggested that the entire total dose difference might be smaller than 2% during treatment under free-breathing. Therefore, we believe that the effect of the respiration phase on the dose evaluation lies within the acceptable range for therapy.

References

1. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, Karasawa K, Hayakawa K, Niibe Y, Takai Y, Kimura T, Takeda A, Ouchi A, Hareyama M, Kokubo M, Kozuka T, Arimoto T, Hara R, Itami J, Araki T. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery?. Int J. Radiat Oncol Biol. Phys. 2011; 81:1352-58.
2. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010; 303:1070-76.
3. Shirato H, Onimaru R, Ishikawa M, Kaneko J, Takeshima T, Mochizuki K, Shimizu S, Umegaki K. Real-time 4-D radiotherapy for lung cancer. Cancer Sci 2011; 103:1-6.
4. Bengua G, Ishikawa M, Sutherland K, Horita K, Yamazaki R, Fujita K, Onimaru R, Katoh N, Inoue T, Onodera S, Shirato H. Evaluation of the Effectiveness of the Stereotactic Body Frame in Reducing Respiratory Intrafractional Organ Motion Using the Real-Time Tumor-Tracking Radiotherapy System. Int J. Radiat Oncol Biol. Phys. 2010;77:630-36
5. Onishi H, Kawakami H, Marino K, Komiyama T, Kuriyama K, Araya M, Saito R, Aoki S, Araki T. A simple respiratory indicator for irradiation during voluntary breath holding: a one-touch device without electronic materials. Radiology 2010;255:917-23
6. Shirato H, Shimizu S, Shimizu T, Nishioka T, Miyasaka K. Real-time tumour-tracking radiotherapy. Lancet 1999; 353:1331-32.
7. Berbeco RI, Nishioka S, Shirato H, Chen GT, Jiang SB. Residual motion of lung tumours in gated radiotherapy with external respiratory surrogates. Phys Med Biol.2005;50:3655-67
8. Hunjan S, Starkschall G, Prado K, Dong L, Balter P. Lack of Correlation Between External Fiducial Positions and Internal Tumor Positions During Breath-Hold CT. Int J Radiat Oncol Biol Phys. 2010;76: 1586-91
9. Yamazaki R, Nishioka S, Date H, Shirato H, Koike T, Nishioka T. Investigation of the change in marker geometry during respiration motion: a preliminary study for dynamic-multi-leaf real-time tumor tracking. Radiation Oncology; 7:218-22.

10. Chang D, Liu C, Dempsey JF, Palta JR, Kopea J, Louis D, Morris C, Chopra R, Olivier KR. Predicting changes in dose distribution to tumor and normal tissue when correcting for heterogeneity in radiotherapy for lung cancer. Am J Clin Oncol. 2007; 30:57-62
11. Chow JC, Leung MK, Van Dyk J. Variations of lung density and geometry on inhomogeneity correction algorithms: A Monte Carlo dosimetric evaluation. Med Phys. 2009;36:3619-30
12. Aarup LR, Nahum AE, Zacharatou C, Juhler-Nøttrup T, Knöös T, Nyström H, Specht L, Wieslander E, Korreman SS. The effect of different lung densities on the accuracy of various radiotherapy dose calculation methods: Implications for tumour coverage. Radiotherapy and Oncology 2009;91:405-14
13. Fragoso M, Wen N, Kumar S, Liu D, Ryu S, Movsas B, Munther A, Chetty IJ. Dosimetric verification and clinical evaluation of a new commercially available Monte Carlo-based dose algorithm for application in stereotactic body radiation therapy (SBRT) treatment planning. Phys Med Biol. 2010;55:4445-64
14. Plathow C, Zimmermann H, Fink C, Umathum R, Schöbinger M, Huber P, Zuna I, Debus J, Schlegel W, Meinzer HP, Semmler W, Kauczor HU, Bock M. Influence of different breathing maneuvers on internal and external organ motion: use of fiducial markers in dynamic MRI. Int J Radiat Oncol Biol Phys.2005;62:238-45
15. Mexner V, Wolthaus JW, van Herk M, Damen EM, Sonke JJ. Effects of respiration-induced density variations on dose distributions in radiotherapy of lung cancer. Int J. Radiat Oncol Biol. Phys. 2009;74:1266-75
16. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, Perez CA. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol. Phys. 1999;45:323-29
17. Barriger RB, Forquer JA, Brabham JG, Andolino DL, Shapiro RH, Henderson MA, Johnstone PA, Fakiris AJ. A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. Int. J. Radiat Oncol Biol. Phys. 2012;82:457-62
18. Jo IY, Kay CS, Kim JY, Son SH, Kang YN, Jung JY, Kim KJ. Significance of low-dose radiation distribution in development of radiation pneumonitis after helical-tomotherapy-based hypofractionated radiotherapy for pulmonary metastases. J Radiat Res.2013;1-8

19. Admiraal MA, Schuring D, Hurkmans CW. Dose calculations accounting for breathing motion in stereotactic lung radiotherapy based on 4D-CT and the internal target volume. 2008;86:55-60
20. Tian Y, Wang Z, Ge H, Zhang T, Cai J, Kelsey C, Yoo D, Yin FF. Dosimetric comparison of treatment plans based on free breathing, maximum, and average intensity projection CTs for lung cancer SBRT. Med Phys. 2012;39:2754-60

Figure legends

Fig.1 Measurement points in CT images (example of ROIs).
(a) Three slices for measuring: the upper slice is located at the midpoint between the tracheal bifurcation and the lung apex; the middle slice is at the tracheal bifurcation; and the lower slice is at the midpoint between the tracheal bifurcation and the lung base. (b) Three locations in a slice: anterior, exterior, and posterior.

Fig.2 Maximum chest wall motion (displacement) and variation of CT value.
(a) Maximum chest wall motion and (b) variation of the mean CT value are plotted as a function of the lung volume inhalation/exhalation (I/E) ratio. The coefficients of correlation are 0.82 for the maximum chest wall motion and 0.78 for the variation of the CT value.

Fig.3 Variation of CT value between inhalation and exhalation.
The mean CT values are indicated for nine locations. A statistically significant difference in the variation is observed in every ROI between inhalation and exhalation ($p<0.05$, paired t-test).

Fig.4 Total dose difference at the isocenter.
Difference of the total dose at the isocenter for each lung volume I/E ratio is within ±2% in the inhalation and exhalation phases.

Fig.5 Dose difference for each field at the isocenter.
A statistically significant difference in the dose difference is observed between inhalation (a) and exhalation (b) ($p<0.05$, paired t-test). If the maximum of the chest wall motion is divided into two parts at 10 mm, a statistically significant difference can be observed between motions below 10 mm and above 10 mm ($p<0.05$, paired t-test).

Fig.6 Difference in volume (exhalation minus inhalation).
(a) Difference of V20 (E-I) and (b) difference of V5 (E-I) are shown as a function of the lung volume I/E ratio. (V20: the volume of the lung receiving 20 Gy, V5: the volume of the lung receiving 5 Gy) As the lung volume I/E ratio increases, the difference of V20 (E-I) and the difference of V5 (E-I) seem to be larger. The coefficients of correlation are 0.80 for V20 (E-I) and 0.84 for V5 (E-I).

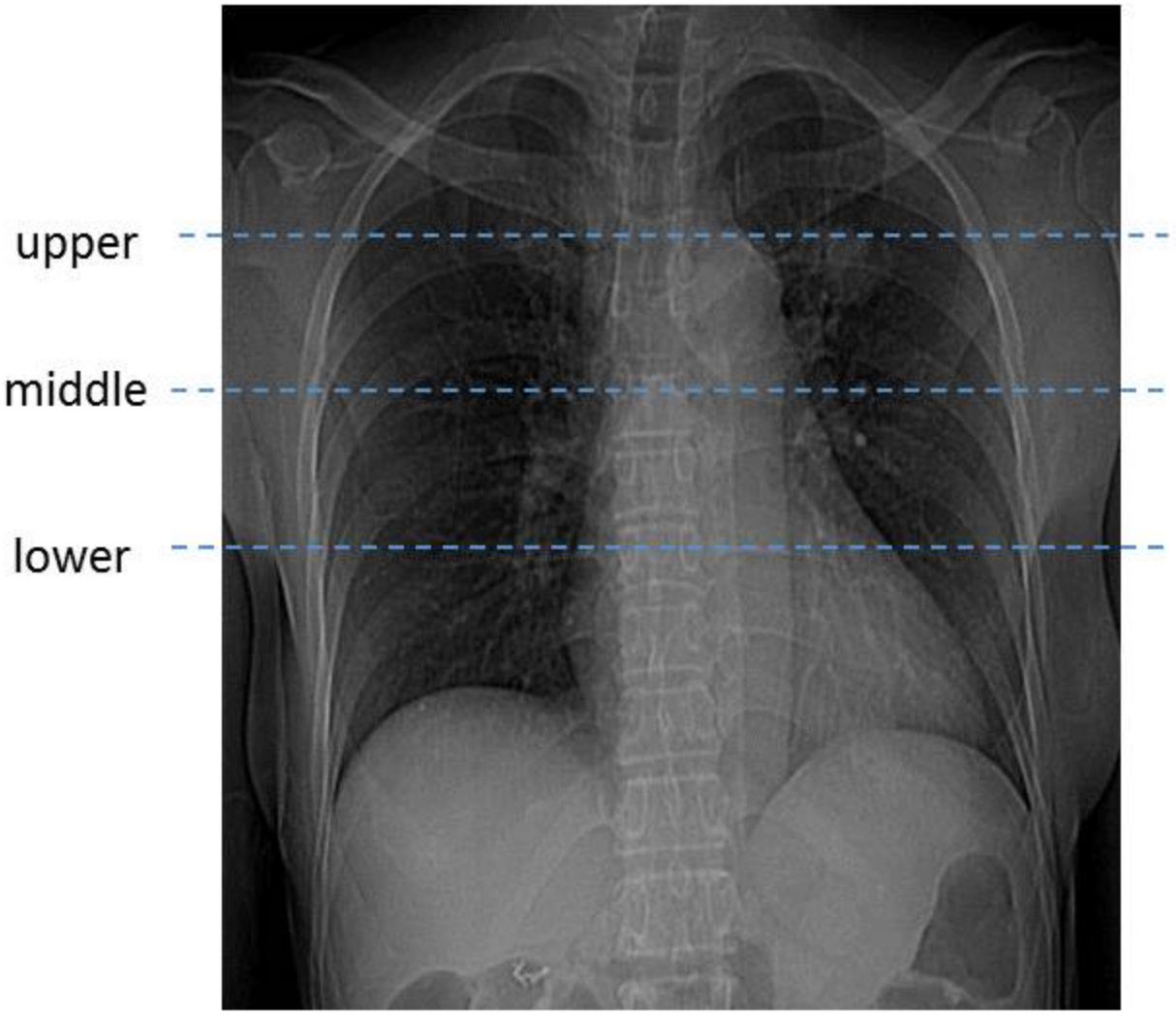

Fig.1(a)

Yamazaki et al.

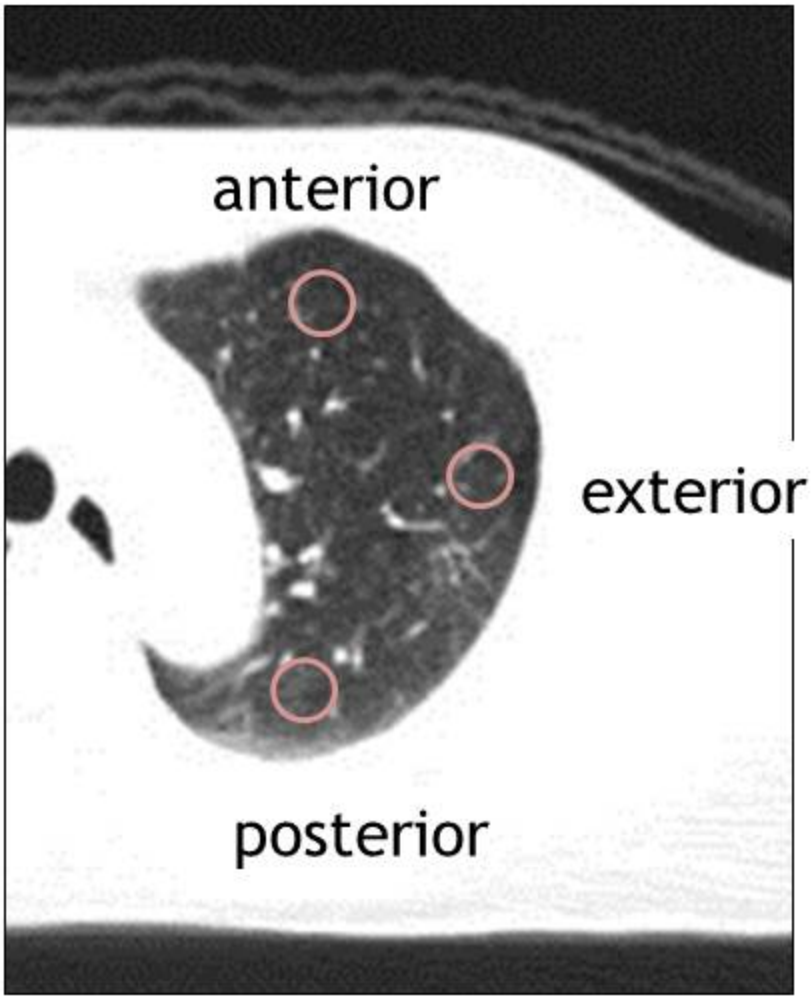

Fig.1(b)

Yamazaki et al.

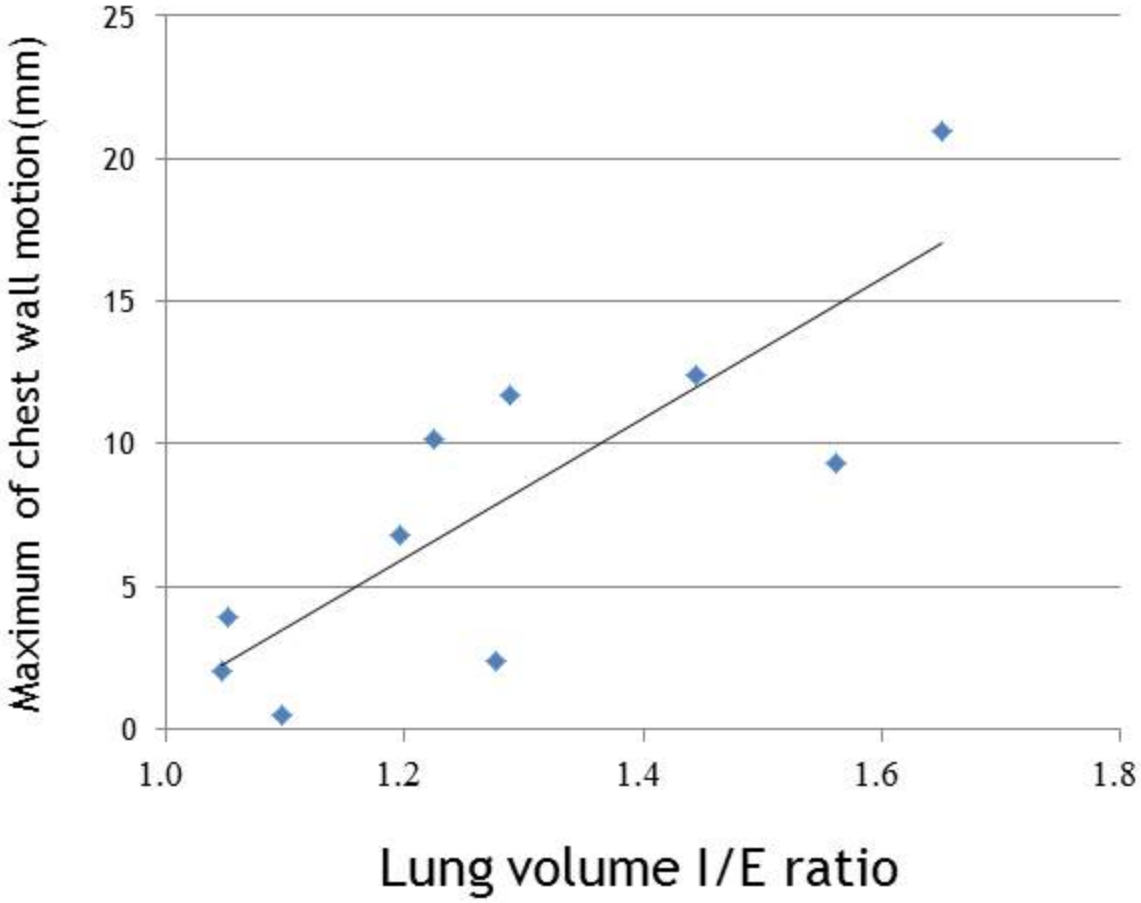

Fig.2(a)

Yamazaki et al.

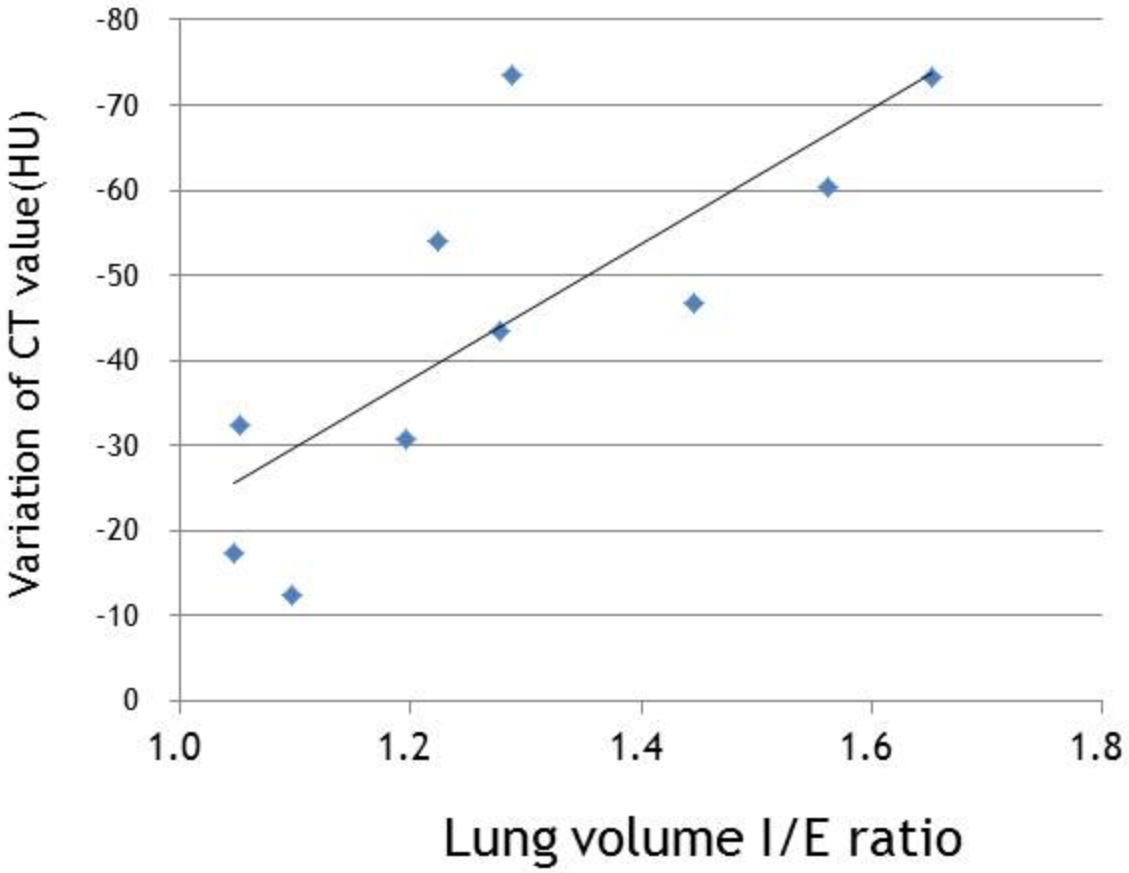

Fig.2(b)

Yamazaki et al.

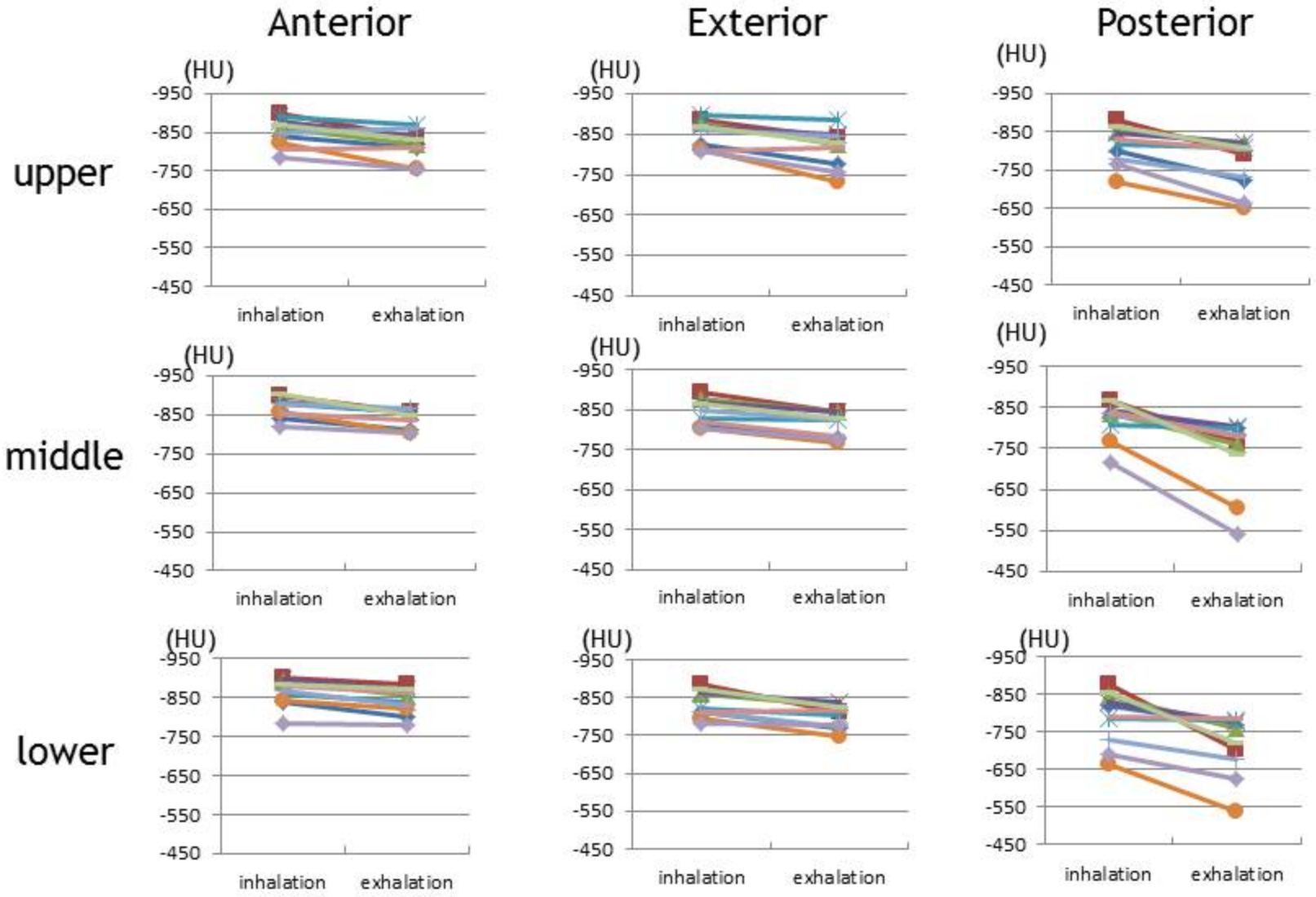

Fig.3
Yamazaki et al.

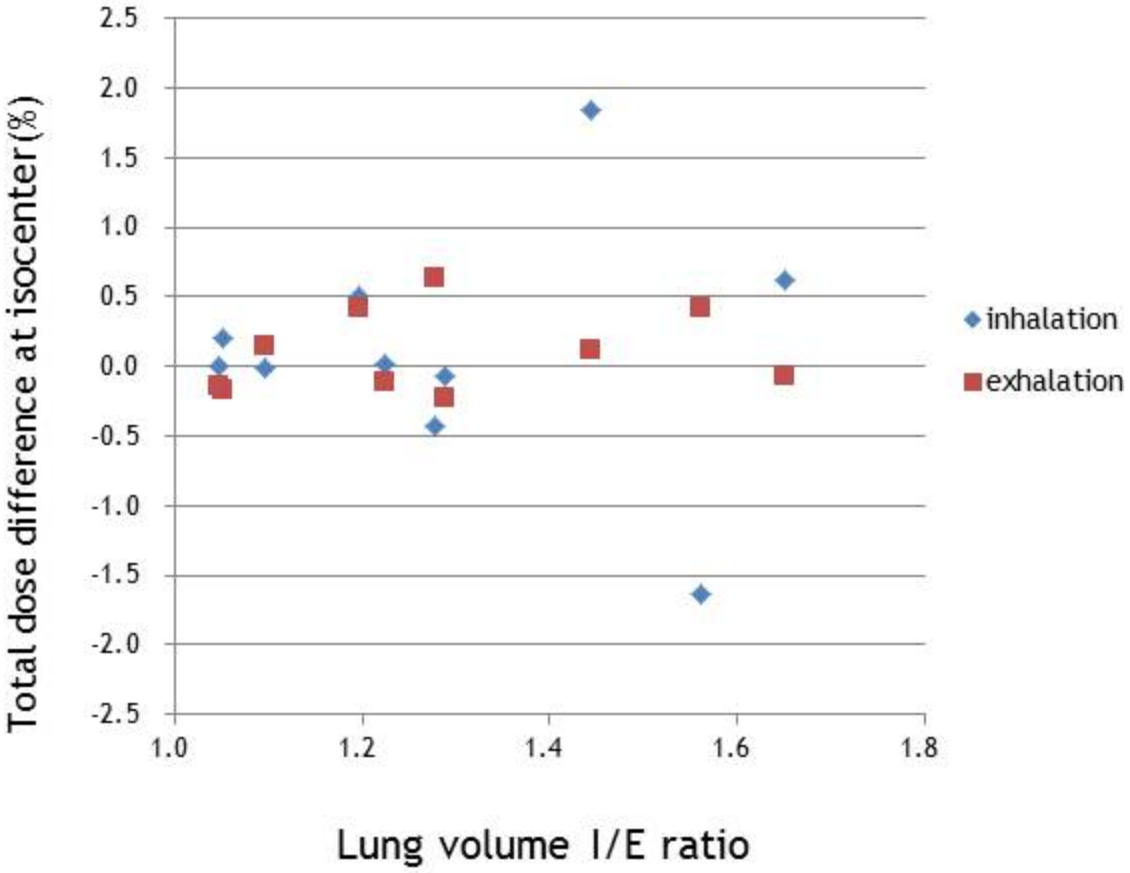

Fig.4

Yamazaki et al.

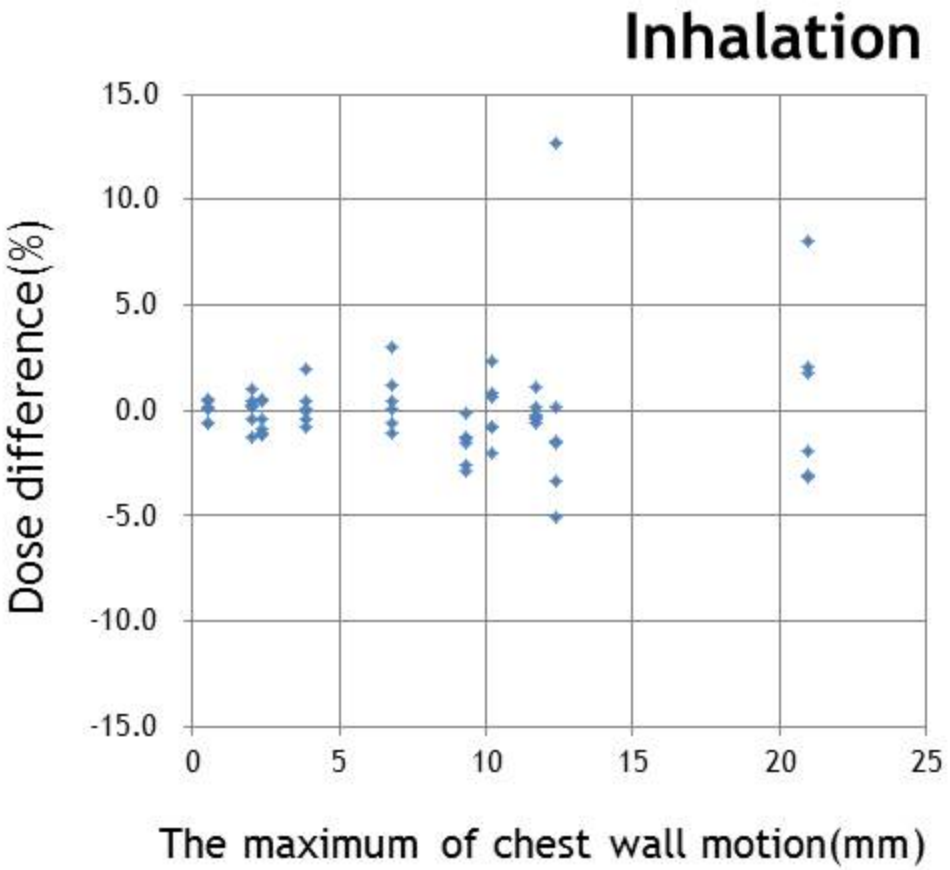

Fig.5(a)

Yamazaki et al.

Fig.5(b)

Yamazaki et al.

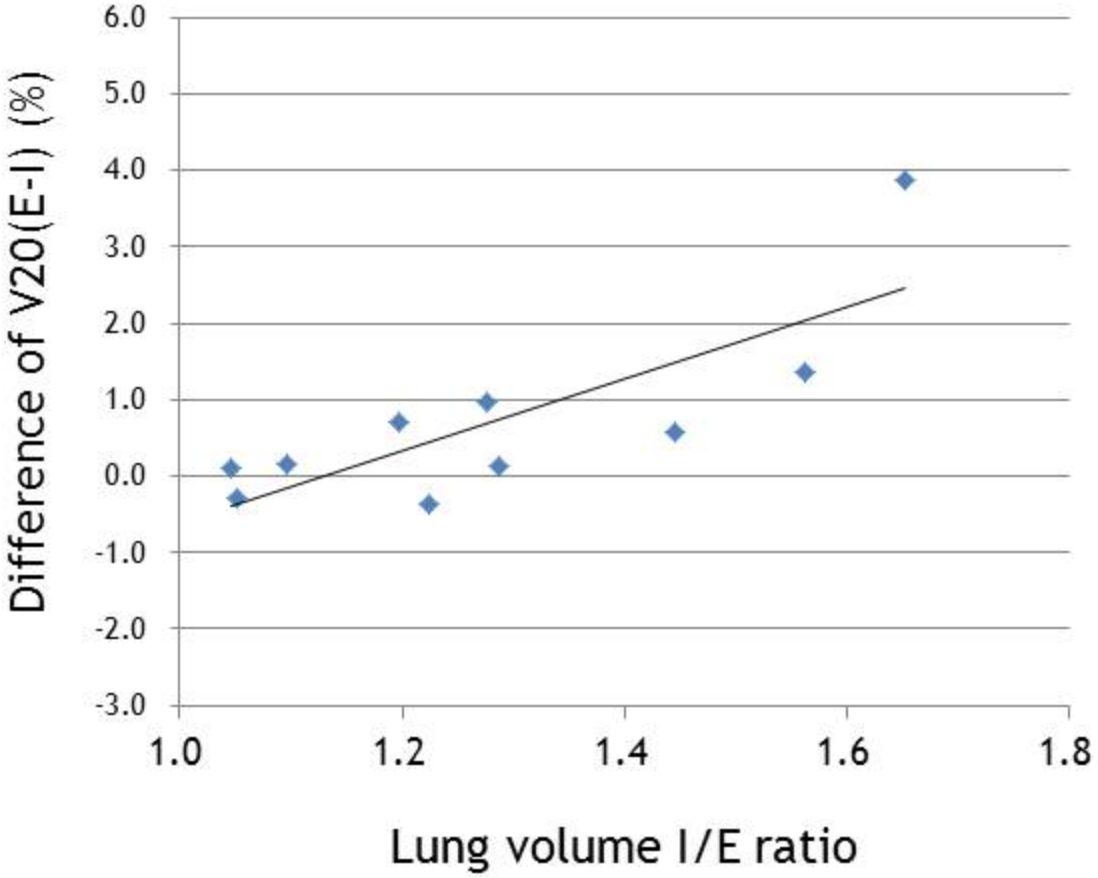

Fig.6(a)

Yamazaki et al.

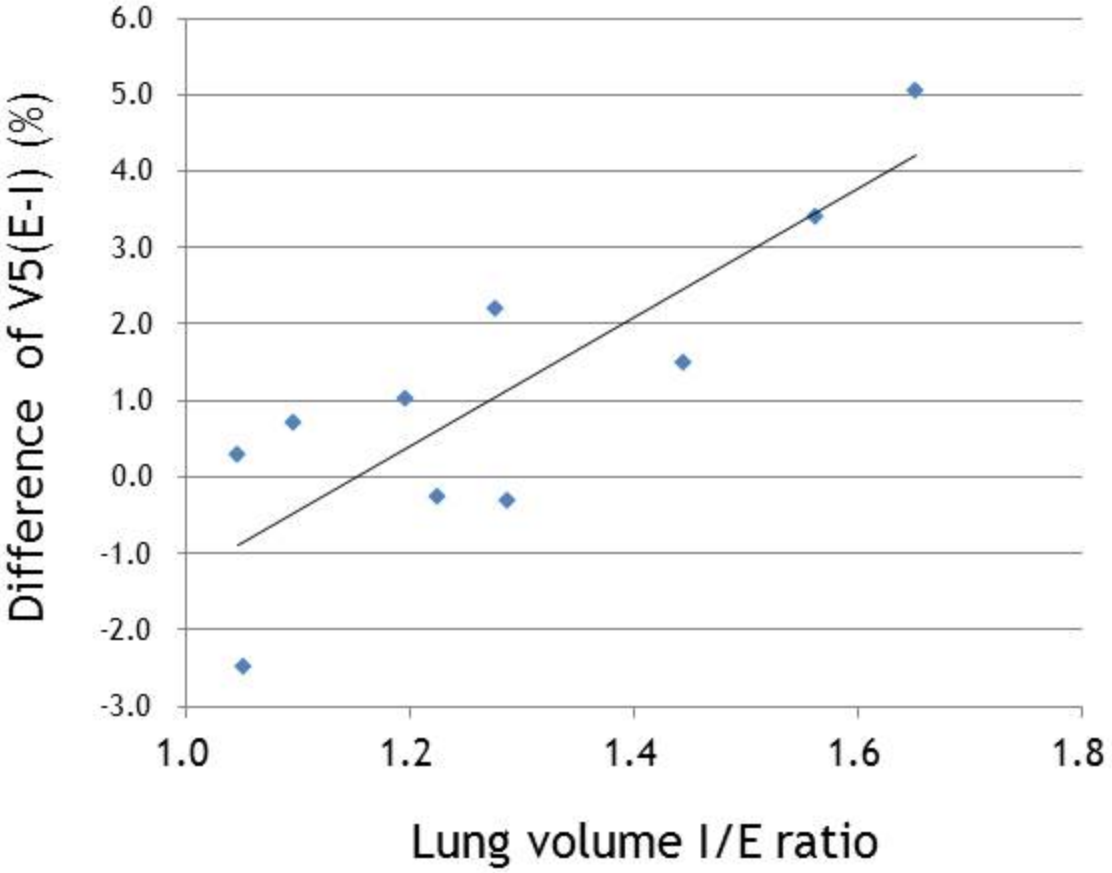

Fig.6(b)

Yamazaki et al.