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Original research article

# Interfractional diaphragm changes during breath-holding in stereotactic body radiotherapy for liver cancer

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ABSTRACT

*Aim and background:* IGRT based on bone matching may produce a large target positioning error in terms of the reproducibility of expiration breath-holding on SBRT for liver cancer. We evaluated the intrafractional and interfractional errors using the diaphragm position at the end of expiration by utilising Abches and analysed the factor of the interfractional error.
*Materials and methods:* Intrafractional and interfractional errors were measured using a couple of frontal kV images, planning computed tomography (pCT) and daily cone-beam computed tomography (CBCT). Moreover, max–min diaphragm position within daily CBCT image sets with respect to pCT and the maximum value of diaphragm position difference between CBCT and pCT were calculated.
*Results:* The mean ± SD (standard deviation) of the intra-fraction diaphragm position variation in the frontal kV images was 1.0 ± 0.7 mm in the C-C direction. The inter-fractional diaphragm changes were 0.4 ± 4.6 mm in the C-C direction, 1.4 ± 2.2 mm in the A-P direction, and −0.6 ± 1.8 mm in the L-R direction. There were no significant differences between the maximum value of the max–min diaphragm position within daily CBCT image sets with respect to pCT and the maximum value of diaphragm position difference between CBCT and pCT.

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*Conclusions:* Residual intrafractional variability of diaphragm position is minimal, but large interfractional diaphragm changes were observed. There was a small effect in the patient condition difference between pCT and CBCT. The impact of the difference in daily breath-holds on the interfractional diaphragm position was large or the difference in daily breath-holding heavily influenced the interfractional diaphragm change.



## 1. Background and aim

Stereotactic body radiation therapy (SBRT) of liver cancer has been undergoing technical changes to improve local control and reduce the normal tissue dose.[1,2] With such dose conformality, high-dose radiation delivered using a high dose per fraction provides an increased chance of tumour control. Accurate daily localisation of the treatment target is very important because of large-dose irradiation in a short period of time.[3,4]

However, SBRT treatment has some problems related to treatment planning.[5,6] Especially, there is a significant interfractional and intrafractional organ motion induced by respiration.[7,8] Liver motion secondary to breathing is one of the largest sources of internal organ motion. There are several methods for coordinating respiratory motion such as controlling the motion through abdominal compression,[9] breath-holding techniques,[10,11] respiratory gating,[12,13] and real-time tumour tracking.[14]

Self-breath-holding in the end-expiration method using a spirometer with reference to the report on breath-holding at end-expiration has a good reproducibility in the breath-holding position, compared with breath-holding at end-inspiration.[15] In our previous study, it was found that IGRT based on bone matching could produce large target positioning errors and diaphragm-based IGRT with breath-holding at end-expiration would be an alternative image matching technique for determining liver tumour position.[16] In our study, we evaluated the interfractional error using diaphragm position, not Lipiodol. There is a possibility to underestimate the respiratory movement in the analysis using Lipiodol because the respiratory movement is different due to the position of the liver. Thus, it is not be said to be evaluated equally for all patients in terms of analysis of interfractional respiratory movement. Moreover, we did not discuss the factor of the interfractional diaphragm variation of respiratory motion. The interfractional variation was caused by systematic and random uncertainties. The systematic uncertainties were determined as the difference in the distances between the position of diaphragm in the planning CT (pCT) data set and the position of diaphragm in the daily CBCT data set. Random uncertainties were determined as the daily difference in the diaphragm positions. In the treatment planning, most of the patients underwent volumetric dynamic contrast-enhanced CT. However, they did not undergo CBCT with contrast enhancement. This condition was one of the main differences between the pCT and daily CBCT tests.

The objectives of this study are the following: to evaluate the interfractional error using the diaphragm position as the surrogate of the tumour at end-expiration by utilising Abches and analyse the factor of the interfractional error.

## 2. Materials and methods

### 2.1. *Patient background*

Between July 2010 and April 2013, 59 patients underwent RT planning and treatment as a part of SBRT for liver cancer cases. The patients' age ranged from 49 to 90 years (mean: 72 years).

### 2.2. *Abches monitoring*

Breath-holding was coordinated in the expiratory phase by using Abches (Apex Medical, Tokyo, Japan), which allows patients to control their chest and abdominal respiratory motions. Fig. 1 shows the procedure implemented for respiratory control using the Abches system. All the patients were advised to hold their breath during the treatment and were informed about the importance of reproducing the tumour position by a radiation technologist. Next, the patients were trained on holding their breath.

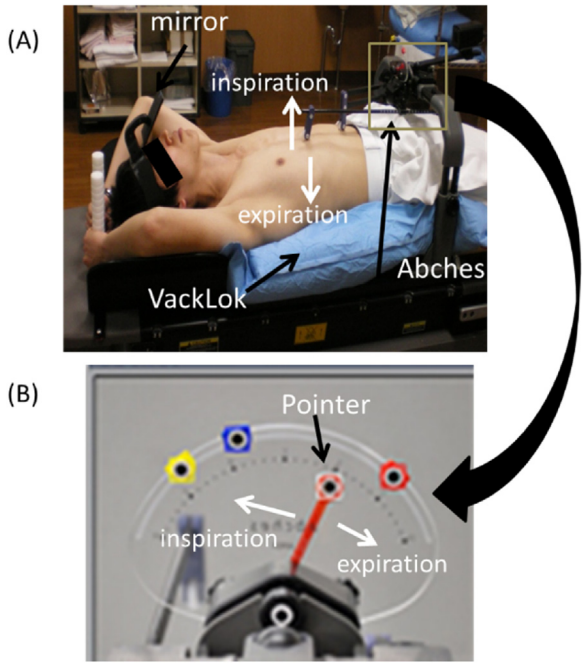


**Fig. 1 – Procedure for respiratory control using the Abches system. (A) Patient position using Abches. (B) Monitor window of Abches.**

### 2.3. Planning

The patient was placed in a supine position on an X-ray simulator (Varian Medical Systems, Palo Alto, CA, USA). The intra-fraction diagram position variation during several expiratory breath-holding intervals was verified to be within 5 mm using a couple of frontal kV-images in the cranio–caudal (C-C) direction. A CT scanner (Lightspeed RT16, GE Healthcare, Little Chalfont, UK) was used to perform CT scans during breath-holding. The slice thickness and the interval were 1.25 mm. The CT volume data were transferred to a treatment planning system (Pinnacle 3 version 9.2, Phillips Medical Systems, Fitchburg, WI, USA). The gross tumour volume (GTV), defined as the tumour volume containing Lipiodol remains after transcatheter arterial chemoembolization (TACE), exhibited early enhancement in the arterial phase of the dynamic CT. The clinical target volume (CTV) margin was defined as 0–5 mm around the GTV. Generally, a planning target volume (PTV) margin of 5–8 mm is added, which includes the respiratory motion reproducibility and setup errors. Eight non-coplanar IMRT fields delivered by a Varian linac were used for all the patients. Treatment plans with a dose of 48 Gy in 4 fractions or 60 Gy in 8 fractions were prescribed to the isocenter, and the dose was calculated using the Clarkson algorithm on Pinnacle[3] (Phillips Medical Systems, Fitchburg, WI, USA). A linear accelerator was used TrueBeam and Clinac iX (Varian Medical Systems, Palo Alto, CA, USA) with 6 MV or 10 MV. The beam directions were aligned to avoid risk to organs such as the liver, spinal cord, right kidney, and duodenum. The dose delivery time was approximately 15 min, which was the same as that in the previous study.[17]

### 2.4. Image verification of the treatment

Using Abches, the patient was coached to perform expiratory breath-holding exactly before scanning. Then, the intra-fraction diagram position variation was confirmed within 5 mm in the couple of frontal kV-images in C-C direction.

CBCT acquisition was performed for several breath-holds, and each scan comprised of 650 obtained projections covering a full rotation angle of 360°. CBCT was performed by splitting the gantry rotation into several breath-holds, and each breath-hold was ~15 s, with intermittent short breaks of free breathing.[18] The acquisition was started after the patient had been coached to perform end-expiration breath-hold; then, it was interrupted by turning off the kV source after the gantry had rotated approximately 90°. While the patient resumed normal breathing, the software that controlled the acquisition computed and displayed the position of the gantry when it was stopped. The acquisition should be resumed from this point. The gantry was rotated back, the patient was coached to perform end-expiration breath-hold again, and the acquisition was restarted. It was interrupted again when the gantry had rotated approximately 180°. The acquisition was resumed in exactly the same way as before and allowed to reach completion. All projections were processed using a Varian On-Board Imager software. The 3D–3D match software provided with the CBCT enabled the user to register the CBCT volume image with the contours that were drawn using the reference CT. This 3D–3D match was performed using a rigid registration technique. The 3D–3D match software also computed the anterior–posterior (A-P), left–right (L-R), and C-C shifts to move the patient to the planned isocenter. The differences between pCT and CBCT are not due to the absence of a contrast medium in IGRT session.

### 2.5. Data analysis

In the analysis of the intrafractional diaphragm change, image verification was performed using kV-images. The maximum difference of the most diaphragm position between each breath-hold was analysed. In the analysis of the interfractional diaphragm variation, image verification of daily CBCT images and pCT images in the offline review (Varian Medical Systems, Palo Alto, CA, USA) was performed using two methods: bone structure matching (bone matching) and diaphragm surface matching (diaphragm matching). The interfractional diaphragm variation investigated in this study was the change of mean diaphragm position by the diaphragm matching relative to bony structures by the bone matching between each treatment session from the changes CBCT to pCT. Daily CBCT images were scanned on 260 treatment fractions. The 6 patients received 60 Gy in 8 fractions and 53 patients received 48 Gy in 4 fractions. During the verification, the window level was 275 HU and the window width was 1300 HU in pCT and CBCT.

#### 2.5.1. Intrafraction diagram position variation

Intra-fraction diagram position variation affects the CBCT image with several breath-holds. We scanned the frontal kV-images alone because the respiratory movement was dominant in the C-C direction as shown in a previous study.[18] The intra-fraction diagram position variation was only evaluated in the C-C direction during breath-holding using a couple of frontal kV-images.

#### 2.5.2. Interfractional diaphragm changes

The interfractional diaphragm changes were the change of mean diaphragm position by the diaphragm matching relative to bony structures by the bone matching between each treatment session from the changes CBCT to pCT in the C-C, A-P, and L-R directions.

#### 2.5.3. The factor of the inter fractional diaphragm changes

We considered the factor of the interfractional diaphragm changes to be the following two items. One is the max–min diaphragm position within daily CBCT image sets with respect to pCT. These were calculated as the deviation between the maximum and minimum diaphragm positions with daily CBCT image sets. The other is the maximum value of diaphragm position difference between CBCT and pCT. We compared the factor of the max–min diaphragm position within daily CBCT image sets with respect to pCT and the maximum value of diaphragm position difference between CBCT and pCT.

### 2.6. Statistical analysis

The data were compared using Student's *t*-test. This test was used to compare the factor of the max–min diaphragm

**Table 1 – Intrafractional diaphragm variations in the C-C direction using a couple of frontal kV-images in 59 patients. The mean (ΔM), standard deviation (SD), minimum (Min) and maximum (Max) interfractional diaphragm changes were shown.**

| | |
|---|---|
| ΔM | 1.0 mm |
| SD | 0.7 mm |
| Min | 0.0 mm |
| Max | 3.1 mm |

position within daily CBCT image sets with respect to pCT and the maximum value of diaphragm position difference between CBCT and pCT. All statistical analyses were performed using IBM SPSS Statistics for Windows (SPSS, IBM, Japan). The statistical significance was defined when the *p*-value was <0.05.

## 3. Results

### 3.1. *Intrafraction diagram position variation*

The intrafractional changes in the diaphragm position changes are displayed graphically in Table 1. The mean absolute diaphragm position change for the C-C direction was 1.0 ± 0.7 mm. All the diaphragm positions were within 3.1 mm.

### 3.2. *Interfractional diaphragm changes (diaphragm matching for bone matching)*

Fig. 2 and Table 2 present the result of the interfractional diaphragm changes relative to the vertebrae position. All the fractions were within ±8 mm in the A-P direction, ±15 mm in the C-C direction, and ±6 mm in the L-R direction. The interfractional diaphragm change was the largest in the C-C direction.

### 3.3. *The factor of the inter fractional diaphragm changes*

Fig. 3 and Table 3 present a comparison of the max–min diaphragm position within daily CBCT image sets with respect to pCT and the maximum value of diaphragm position difference between CBCT and pCT. The maximum value of the max–min diaphragm position within daily CBCT image sets with respect to pCT and the maximum deviations of the diaphragm position between pCT and CBCT were 24 mm and 15 mm in the C-C direction, 9 mm and 8 mm in the A-P direction, and 13 mm and 7 mm in the L-R direction, respectively. The mean ± SD of the max–min diaphragm position within daily CBCT image sets with respect to pCT and the deviation of the diaphragm position between pCT and CBCT were 6.4 ± 4.6 mm and 5.8 ± 3.7 mm in the C-C direction, 2.8 ± 1.9 mm and 3.2 ± 1.9 mm in the A-P direction, and 2.7 ± 2.1 mm and 2.4 ± 1.4 mm in the L-R direction, respectively. The change was the largest in the C-C direction in both methods. The results of *p*-value from the *t*-test were 0.2 in the C-C direction, 0.1 in the A-P direction, and 0.3 in the L-R direction. There were no significant differences between the maximum value of the max–min diaphragm position within daily CBCT image sets with respect to pCT and the maximum value of diaphragm position difference between CBCT and pCT.

## 4. Discussion

We evaluated the interfractional error using the diaphragm position at end-expiration by utilising Abches and analysed the factor of the interfractional error for liver SBRT. The intrafraction diagram position variation was within 3.1 mm, which was the same as that of the intra-fractional uncertainties in the 3D tumour position in previous studies.[19,20] Moreover, the interfractional uncertainty in tumour position was 0.4 ± 4.6 m in the C-C direction. It was also the same as that of the interfractional uncertainty in the past study that was 1.4 ± 4.3 mm in the C-C direction using deep inspiration breath-holding technique (DIBH) with Real-time Position Management (RPM, Varian Medical Systems, Palo Alto, CA, USA).[20] The interfractional variation was large as compared to the intrafractional variation. From above, it was difficult to control the interfractional diaphragm position with DIBH and breath-holding at end-expiration with Abches. The factors causing a large interfractional diaphragm variation are considered to be due to the difference in daily breath-holding at the end of expiration, difference in breath-holding positions with Abches on each breath-hold, and daily condition of the patient. In a previous study on intra- and interfraction variability in the tumour motion amplitude without breath-holding, the mean systematic change in the daily mean was 4.97 mm in the C-C direction.[19] In the current study, the systematic change in the daily mean was 4.6 mm from the result of Table 2. This suggests that interfractional diaphragm variation is not dependent on the respiratory control techniques. From above, the main factor causing a large interfractional diaphragm could be the difference in daily condition of the patient.

Tarohda et al. showed that respiratory control with Abches achieved high accuracy and reproducibility although they analysed the Lung SBRT patients under free breath condition without using the Abches system.[21]

The breath-holding position was affected by the daily respiratory motion. The breath-holding position (red marker on Abches, as shown in Fig. 1(B)) was set by the radiation technologist after considering the patient's daily respiratory motion. The patient's condition during the treatment planning was different from that during the treatment. The patient was tense during the planning CT because the patient was performing breath-holds with Abches for the first time. Moreover, the patient was administered the contrast medium because of which the patient was fasting and the contrast could have caused a side effect. However, there were no significant differences between the max–min diaphragm position within daily CBCT image sets with respect to pCT and the maximum value of diaphragm position difference between CBCT and pCT. This suggests that the difference in the patient's conditions has a small influence on the interfractional diaphragm variation at the end of expiration. The past study which used DIBH for

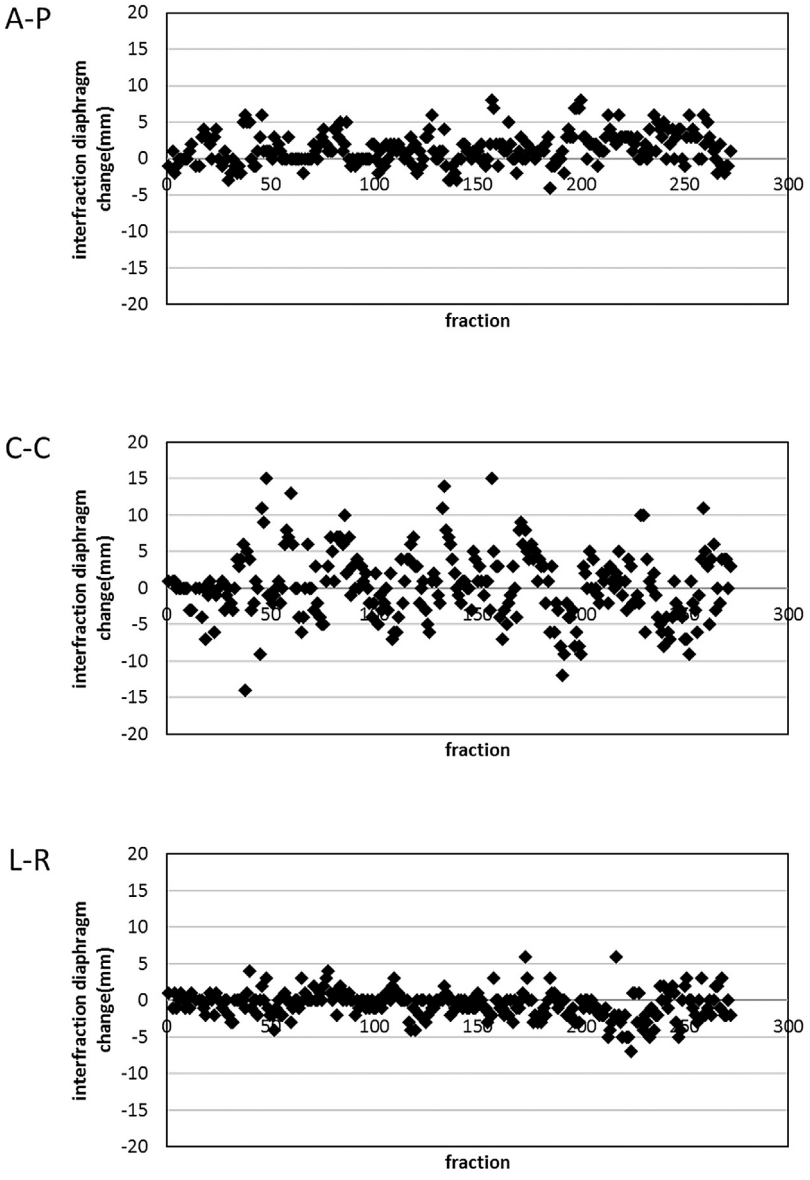


**Fig. 2 – Interfractional diaphragm variations in the A-P, C-C, and L-R directions from the changes CBCT to pCT in 260 fractions of 59 patients.**

**Table 2 – Interfractional diaphragm changes in the A-P, C-C, and L-R directions from the changes CBCT to pCT in 260 fractions of 59 patients. The mean (ΔM), standard deviation (SD), minimum (Min) and maximum (Max) interfractional diaphragm changes were shown.**

| | A-P | C-C | L-R |
|---|---|---|---|
| ΔM | 1.4 mm | 0.4 mm | −0.6 mm |
| SD | 2.2 mm | 4.6 mm | 1.8 mm |
| Min | −4.0 mm | −14.0 mm | −7.0 mm |
| Max | 8.0 mm | 15.0 mm | 6.0 mm |

lung SBRT reported the occurrence of tumour base-line shifts in relation to the bony anatomy throughout the RT course.[20] Additionally, they have previously observed large base-line shift in a lesion close to the diaphragm.[22] Our study analysed the diaphragm position for all patients. The effect of the difference in daily breath-holding at the end of expiration is large from the analysis of the factor of the interfractional diaphragm changes.

## 5. Conclusions

Residual intrafractional variability of diaphragm position is minimal, but a large interfractional diaphragm changes were observed using end-expiration breath-holding technique with Abches. This study revealed the factor of interfractional diaphragm changes. There was a small effect in the patient condition difference between pCT and CBCT, but the difference in daily breath-holding had a large effect for interfractional diaphragm changes.

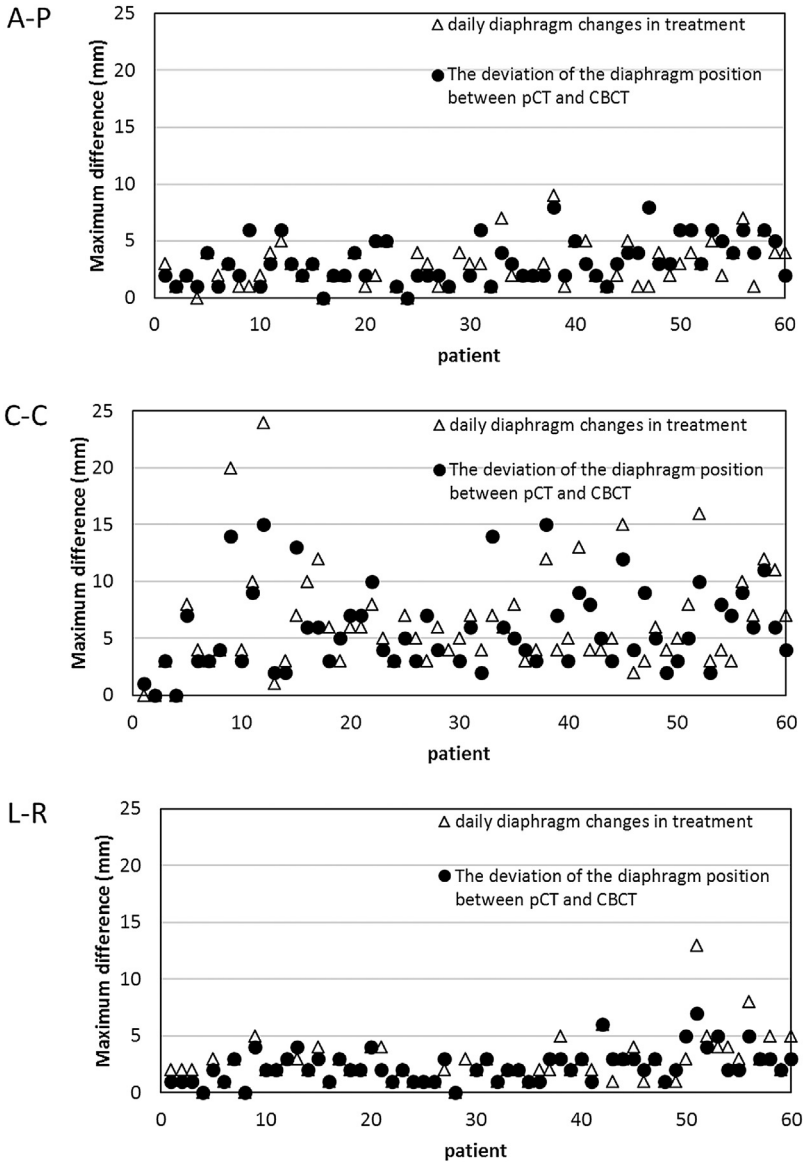


**Fig. 3 – Comparison of the max–min diaphragm position within daily CBCT image sets (daily diaphragm changes in treatment) and the maximum value of diaphragm position difference between CBCT and pCT (the deviation of the diaphragm position between pCT and CBCT) in the A-P, C-C, and L-R directions in 59 patients.**

**Table 3 – The mean ± SD of the max–min diaphragm position within daily CBCT image sets (daily diaphragm changes in treatment) and the maximum value of diaphragm position difference between CBCT and pCT (the deviation of the diaphragm position between pCT and CBCT) in the A-P, C-C, and L-R directions in 59 patients.**

| | C-C | A-P | L-R |
|---|---|---|---|
| Daily diaphragm changes in treatment | 5.8 ± 3.7 mm | 3.2 ± 1.9 mm | 2.4 ± 1.4 mm |
| The diaphragm position between pCT and CBCT | 6.4 ± 4.6 mm | 2.8 ± 1.9 mm | 2.7 ± 2.1 mm |
| *t*-Test | $p > 0.05$ | $p > 0.05$ | $p > 0.05$ |

## Conflict of interest

None declared.

## Financial disclosure

None declared.

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