

# Determination of reproducibility of end-exhaled breath-holding in stereotactic body radiation therapy

Motoharu Sasaki<sup>1,\*</sup>, Hitoshi Ikushima<sup>1</sup>, Kanako Sakuragawa<sup>2</sup>,  
Michihiro Yokoishi<sup>2</sup>, Akira Tsuzuki<sup>3</sup> and Wataru Sugimoto<sup>4</sup>

<sup>1</sup>Department of Therapeutic Radiology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima, Tokushima 770-8503, Japan

<sup>2</sup>Department of Radiological Technology, Tokushima University Hospital, 2-50-1 Kuramoto-cho, Tokushima, Tokushima 770-8503, Japan

<sup>3</sup>Department of Radiological Technology, Kochi Medical School Hospital, 185-1 Kohasu, Oko-cho, Nankoku-shi, Kochi 783-8505, Japan

<sup>4</sup>Department of Radiological Technology, Tokushima Prefectural Central Hospital, 1-10-3 Kuramoto-cho, Tokushima, Tokushima 770-8539, Japan

\*Corresponding author. Department of Therapeutic Radiology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima, Tokushima 770-8503, Japan. Tel: +81-88-633-9053; Fax: +81-88-633-9051; Email: msasaki@tokushima-u.ac.jp  
(Received 1 June 2020; revised 13 July 2020; editorial decision 8 August 2020)

## ABSTRACT

Methods to evaluate the positional reproducibility of breath-hold irradiation mostly require manual operation. The purpose of this study is to propose a method to determine the reproducibility of breath-hold irradiation of lung tumors between fractions using non-artificial methods. This study included 13 patients who underwent terminal exhaled breath-hold irradiation for primary and metastatic lung cancer. All subjects received a prescribed dose of 60 Gy/8 fractions. The contours of the gross tumor volume (GTV) were extracted by threshold processing using treatment-planning computed tomography (CT) and cone-beam CT (CBCT), which was done just before the beginning of the treatment. The method proposed in this study evaluates the dice similarity coefficient (DSC) and Hausdorff distance (HD) by comparing two volumes, the GTV<sub>CTS</sub> (GTV obtained from treatment-planning CT) and GTV<sub>CBCT</sub> (GTV obtained from CBCT). The reference contours for DSC and HD are represented by GTV<sub>CTS</sub>. The results demonstrated good visual agreement for cases with a DSC of  $\sim 0.7$ . However, apparent misalignment occurred when the DSC was  $< 0.5$ . HD was  $> 2$  mm in 3 out of 13 cases, and when the DSC was  $\sim 0.7$ , the HD was  $\sim 1$  mm. In addition, cases with greater HD also demonstrated more significant variability. It was found that the DSC and HD evaluation methods for the positional reproducibility of breath-hold irradiation proposed in this study are straightforward and can be performed without the involvement of humans. Our study is of extreme significance in the field of radiation studies.

**Keywords:** dice similarity coefficient; Hausdorff distance; breath-hold irradiation; lung cancer

## INTRODUCTION

According to the cancer information service of the National Cancer Center, between 1958 and 2018 lung cancer was the most common cause of death among Japanese people [1]. Radiotherapy has become an important treatment option for lung cancer patients. Stereotactic body radiation therapy (SBRT) for lung cancer is a small-fractionated large-dose irradiation method, and the effect of positional reproducibility per dose on clinical outcomes is greater for this irradiation method than for more conventional irradiation methods. Treatment of stage I

non-small cell lung cancer with SBRT has been reported to produce local control and survival rates comparable to surgery [2–4].

However, it has been reported that lung cancer tumors experience respiratory migration and can move up to 2 cm in a single fraction during radiotherapy [5–7]. Therefore, various irradiation techniques, such as respiratory-gated treatments, breath-holding irradiation and tracking irradiation, have reportedly been used in lung cancer radiotherapy to reduce the internal margin [8–12]. The results of a questionnaire survey that was administered by the Quality Assurance Quality

Control committee of the Japan Society of Medical Physics from April to June 2017 revealed that more than half of Japanese institutions that implement measures against respiratory mobility use the breath-hold irradiation technique [13].

In recent years, the use of cone-beam computed tomography (CBCT) for image-guided radiation therapy (IGRT) has made it possible to match the target's position with that of the radiation therapy beam. However, when using CBCT, it is not practical to acquire images during a single breath-hold because the fastest acquisition time still requires >30 s. Therefore, the CBCT acquires images during four to five breath-hold segments. Hence, position reproducibility is important for accurate position matching in breath-hold irradiation. Previous studies have shown good positional reproducibility results for breath-hold irradiation in end exhalation [12, 14, 15]. Although various methods have evaluated the positional reproducibility of breath-hold irradiation, most of them require manual operation. There are a variety of possible sources of uncertainty due to the use of artificial methods. In 2017, the American Association of Physicists in Medicine released the technology for image registration, including deformable image registration (DIR), and issued guidelines for commissioning operating procedures and tolerances. The guidelines stated that when establishing feature points, it could be difficult to define the appropriate correspondence points accurately and adequately.

The purpose of this study is to propose a method to determine the reproducibility of breath-hold irradiation of lung tumors between fractions using a non-human-mediated method. Furthermore, the differences between the proposed method and previous evaluation methods are clarified. Traditionally, the accuracy of breath-hold irradiation alignment is assessed by the accuracy of the center of gravity of the tumor between the treatment planning CT and the CBCT, just before treatment. Other methods of assessment involve identifying differences in the characteristic points of blood vessels and tracheal branches of the lungs. However, our main objective is to understand the misalignment of the entire tumor. One of the methods proposed in this study, the dice similarity coefficient (DSC), allows for the assessment of overall tumor misalignment on treatment-planning CT and CBCT obtained immediately before treatment. Therefore, DSC is an ideal method for evaluating the level of tumor misalignment. However, the accuracy of DSC may vary depending on the tumor size. This is because small tumors may cause the DSCs to be extremely low for small misalignments. However, if the tumor is sufficiently large, our method can be implemented without any error or difficulty. We further propose that the evaluation of the Hausdorff distance (HD) in conjunction with the DSC can compensate for the shortcomings of DSC in the case of small tumors.

## MATERIALS AND METHODS

### Patients

This study included 13 patients who underwent terminal exhaled breath-hold irradiation for primary and metastatic lung cancer between April 2018 and June 2019. The characteristics of the patients are shown in Table 1. In all subjects, the prescribed doses were 60 Gy/8 fractions. Written informed consent was given for the use of the data collected in this study, and the ethics review board of the Clinical Trial Center,

Tokushima University Hospital, approved the study (Approval No. 3434).

### Image acquisition using a treatment-planning CT simulator

All patients underwent image acquisition using the Standard Wing Board MTWB09 (CIVCO Radiotherapy, Orange City, IA, USA) with both arms raised, and a treatment-planning CT simulator (Optima CT580W; General Electric Medical Systems, Waukesha, WI, USA) was also used. A breathing monitoring system, Abches III (APEX medical, Tokyo, Japan), was used to monitor breath-holding. The respiratory control protocol instructed the patients to hold their breath at the end-expiratory stage and moved the mark to a position where the Abches III accessory pointer could be held reproducibly (Fig. 1). The patient can visually see the pointer and mark positions according to the respiratory level by wearing a special mirror. The fulcrum was adjusted so that the operating range of the pointer was appropriate. For image acquisition by a CT simulator, the field of view was 500 mm and the slice thickness was 2.5 mm. The image acquisition was performed in helical mode and the scan time was ~10 s per scan. The patient held their breath for several times only when the area that could be imaged was narrowed in 10 s. The imaging range was set such that multiple breath-holdings was avoided in the area where the tumor was located. The time necessary to enter and exit the CT simulator room was ~1 h and the time provided for patients to practice holding their breath was ~30 min.

### Image acquisition using a CBCT

The fulcrum of the Abches III was set to the same position each time when the patient was aligned just before treatment. In addition, patients practiced breath holding with end exhalation about five times before treatment, and CBCT was taken after the breathing level was stabilized. Since many lung cancer patients are elderly, the reproducibility of breath-holding may deteriorate due to fatigue during IGRT image acquisition and radiotherapy. Therefore, in order to maximize the reproducibility of breath-holding, we decided to only have each patient practice breath-holding five times. The CBCT on the linear accelerator (LINAC) (TrueBeam; Varian Medical Systems, Palo Alto, CA, USA) was used to perform half-scan image acquisition. The LINAC used in this study can rotate 6° per second, but the half-scan requires about 200° of the rotation angle, so it takes about 33 s of imaging time. We divided the images into four to five sessions because it is difficult for a patient to hold one breath during the entire CBCT imaging process. The CBCT used in this study had a time lag between the pressing of the beam-on kV X-ray button and the actual kV X-ray exposure; each patient had one breath hold for about 10 s, although the actual imaging time was about 7 s. Because CBCT imaging was performed immediately before each treatment, all patients underwent eight imaging sessions.

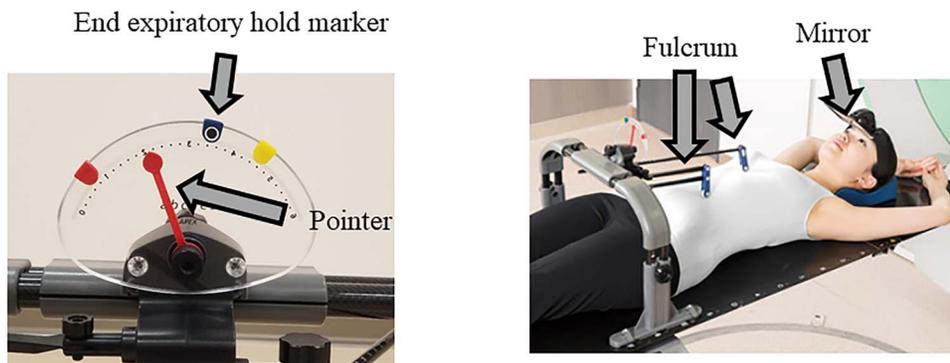
### Proposed and conventional evaluation methods

#### Proposed method

First, we performed rigid registration (RR) based on the bone structure between the CT simulator and the CBCT taken just before treatment using DIR software (Velocity; Varian Medical Systems, Palo Alto, CA,

**Table 1. Patient characteristics**

	Age	Gender	Location	Primary or metastasis	Size (cc)
Case 1	69	Female	Right middle lobe	Primary	17.15
Case 2	84	Male	Left upper lobe	Primary	6.02
Case 3	84	Male	Right middle lobe	Primary	8.5 1
Case 4	81	Male	Right middle lobe	Primary	8.2
Case 5	76	Male	Right middle lobe	Metastasis	0.91
Case 6	70	Female	Right middle lobe	Metastasis	0.81
Case 7	60	Female	Right middle lobe	Metastasis	2.41
Case 8	85	Male	Right middle lobe	Primary	12.26
Case 9	88	Male	Right middle lobe	Metastasis	1.61
Case 10	95	Male	Left upper lobe	Primary	10.23
Case 11	77	Male	Left upper lobe	Primary	3.13
Case 12	50	Female	Left upper lobe	Metastasis	1.17
Case 13	49	Female	Right middle lobe	Metastasis	1.94



**Fig. 1. A breathing monitoring system, Abches III (APEX medical, Tokyo, Japan), was used to monitor breath-holding.**

USA). RR was performed automatically using the area where the vertebrae, sternum and ribs on the affected side of the CBCT are located as the region of interest (Fig. 2a). Next, the contours of the gross tumor volume (GTV) were extracted from the CT simulator and the CBCT taken immediately before the treatment using a threshold process. The GTV<sub>CTS</sub> extracted from the treatment-planning CT simulator by threshold processing was compared with the GTV contours that were manually drawn by a radiation oncologist at the time of the original treatment-planning. The GTV<sub>CBCT</sub> was extracted from the CBCT by threshold processing (Fig. 2b). The method proposed in this study evaluates DSC and HD using two contours, GTV<sub>CTS</sub> and GTV<sub>CBCT</sub>, with GTV<sub>CTS</sub> as the reference contour. The higher the DSC, the closer the value is to 1.

$$DSC(GTV_{CTS}, GTV_{CBCT}) = 2 |GTV_{CTS} \cap GTV_{CBCT}| / (|GTV_{CTS}| + |GTV_{CBCT}|)$$

The distance dH is such that any point of X on GTV<sub>CTS</sub> can reach any point of Y on GTV<sub>CBCT</sub> by advancing a distance of at least dH, and any point of Y on GTV<sub>CBCT</sub> can reach any point X on GTV<sub>CTS</sub> by advancing a distance of at least dH, which is expressed by the following

equation.

$$dH(X, Y) = \max_{x \in X} \{ \min_{y \in Y} \{ d(x, y) \} \}$$

**Conventional method**

Conventional methods to evaluate the reproducibility of breath-hold irradiation employed feature points. Five feature points were set up on the treatment-planning CT simulator and the CBCT images taken just before the treatment (Fig. 3). The characteristic points were set as large vessels or tracheal bifurcations. The setting range is within 5 cm of the center of gravity of the GTVs drawn by the radiation oncologist, which is appropriate for clarifying the difference between the proposed and conventional evaluation methods.

**RESULTS**

**Proposed method**

The DSC results for GTV<sub>CTS</sub> and GTV<sub>CBCT</sub> are shown in Fig. 4. As shown on the Case 1 treatment-planning CT simulator image in Fig. 5, the contours of GTV<sub>CBCT</sub> and GTV<sub>CTS</sub> obtained from the CBCT taken immediately before treatment had a DSC >0.7 (Fig. 5). In addition, the contours of GTV<sub>CBCT</sub> and GTV<sub>CTS</sub> obtained from the CBCT taken immediately before treatment, which has a DSC <0.5, are shown on

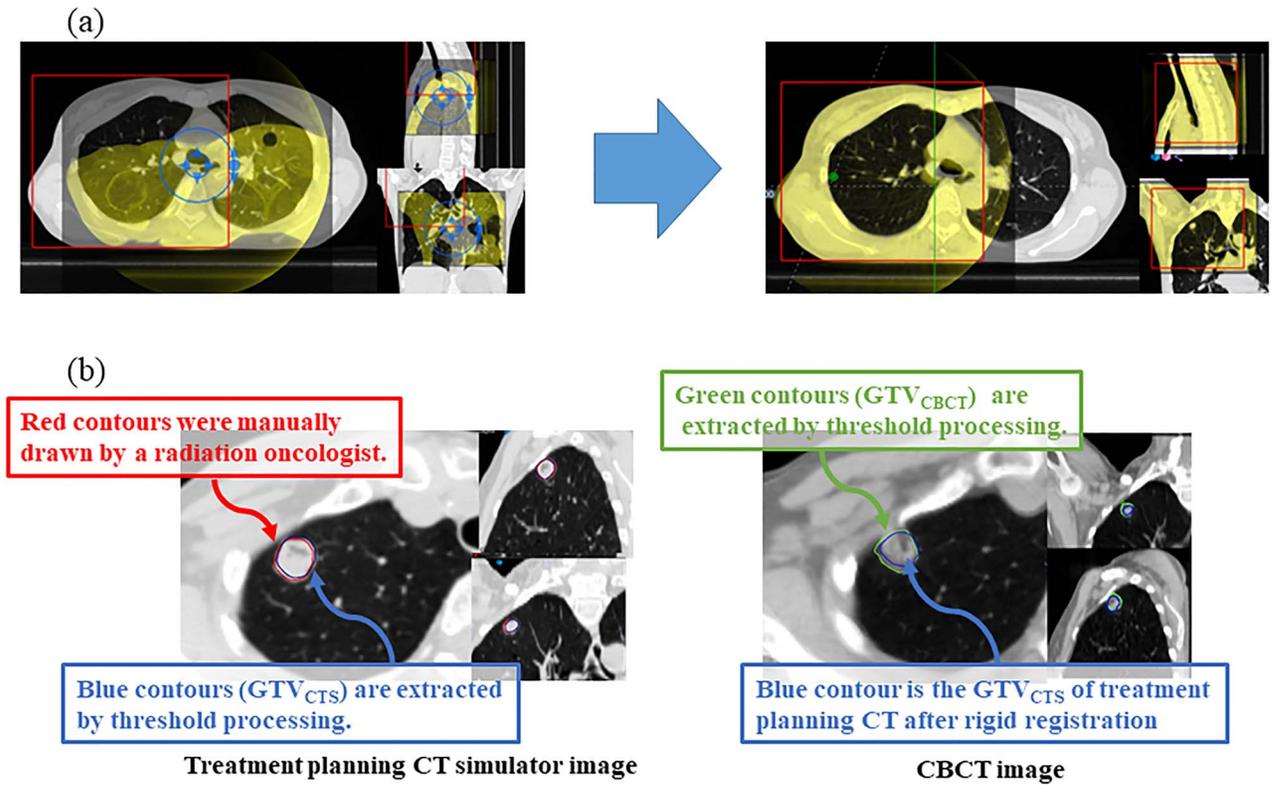


Fig. 2. A proposed method for evaluation of the reproducibility of breath-hold irradiation of lung tumors between fractions using a non-human-mediated method. (a) Treatment-planning CT and CBCT with radiotherapy using the region of interest based on bone structure criteria. (b) Contour extraction using GTV<sub>CTS</sub> and GTV<sub>CBCT</sub> threshold processing.

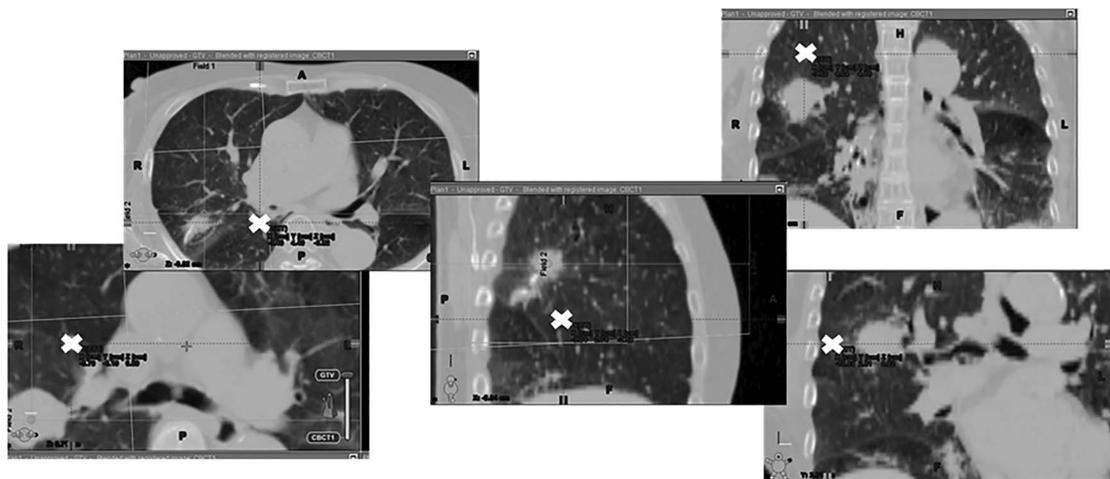


Fig. 3. Treatment-planning CT simulator and CBCT image taken just before treatment with five feature points.

the Case 4 treatment-planning CT simulator image (Fig. 6). These results demonstrate that the visual agreement was good for cases with a DSC of  $\sim 0.7$ , but apparent misalignment occurred when the DSC was  $< 0.5$ .

The GTV<sub>CTS</sub> and GTV<sub>CBCT</sub> HD results are shown in Fig. 7. The HD was  $> 2$  mm in 3 out of 13 cases, and when the DSC was  $\sim 0.7$ , the HD was  $\sim 1$  mm. In addition, cases with greater HD also showed more significant variability.

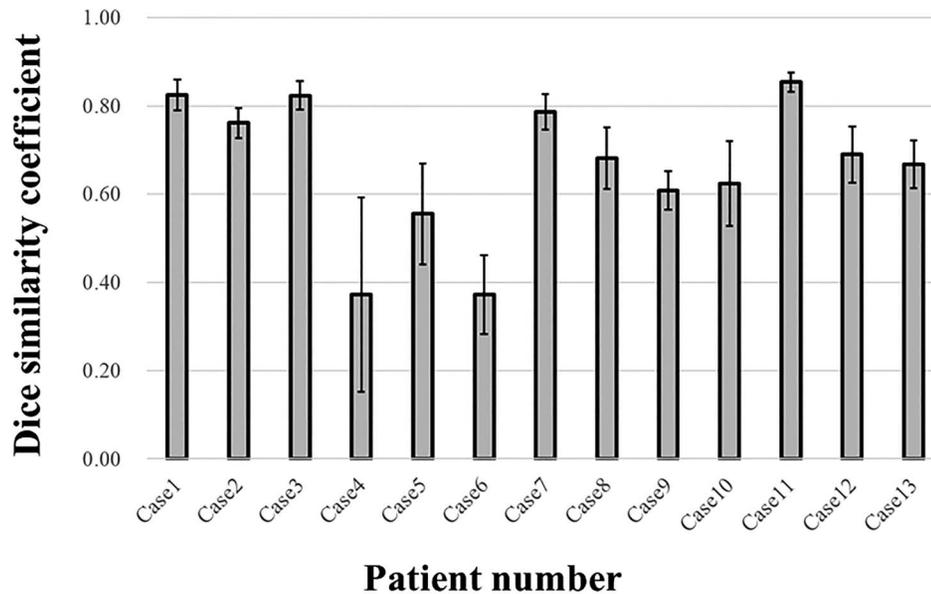


Fig. 4. DSC results for GTV<sub>CTS</sub> and GTV<sub>CBCT</sub>.

### Conventional method

The results of the feature points obtained by the conventional method are shown in Fig. 8. The negative directions are right, inferior and posterior, respectively, in the left–right (L–R), superior–inferior (S–I) and anterior–posterior (A–P) directions, respectively. The results for the reproducibility of the breath-hold irradiation demonstrated that no cases of a 3D misalignment of >5 mm were found except for Case 11 and Case 13. For the cases where HD was >2 mm, the 3D misalignment was also >5 mm.

### DISCUSSION

In this study, evaluation of the feature points using vascular or tracheal bifurcation points demonstrated that 11 of 13 patients exhibited high breath-hold reproducibility that was within 5 mm in the case of 3D distances. Onishi *et al.* [14] compared breath-hold reproducibility obtained using the same breathing monitoring system as in this study to that obtained without the system. The mean maximum differences were 2.0 and 4.2 mm, 1.5 and 2.8 mm, and 1.2 and 2.0 mm in the S–I, A–P and L–R directions, respectively, depending on the presence or absence of the device, indicating that the differences in all directions were significantly smaller with the device than without it ( $P < 0.05$ ). The breath-holding reproducibility obtained in this study using the respiratory monitoring system was 0.18, –0.22 and –0.73 mm in the S–I, A–P and L–R directions, respectively, which was a better result than that reported by Onishi *et al.* [14]. Other studies have reported a breath-hold reproducibility that fell within 5 mm in each direction [17–19]. In the present study, the reproducibility was also within 5 mm in each direction, and so the reproducibility of breath-holding is considered to be comparable to what was previously reported. This study shows that the patients can be irradiated with the same or better breath-hold as those reported in the past. Therefore, the evaluation using

the conventional method proved that there is no significant difference between the cases reported in the previous studies and the present study. In addition, the guidelines of the Japanese Society for Radiation Oncology QA Committee require a reproducibility of patient skeleton of  $\leq 5$  mm [20]. Therefore, assuming positioning by bone reference as shown in Fig. 8, Cases 4 and 6 fail to meet fixation accuracy within 5 mm. The DSC in both cases was  $< 0.4$  and the HD was  $> 2.0$  mm. The advantage of using a combination of DSC and HD, as proposed in this study, is that the volume of the whole tumor can be evaluated. Ideally, when evaluating the irradiation position accuracy of exhaled breath, the entire tumor is displaced. The conventional method cannot evaluate the displacement of the entire tumor because it is a feature point. For cases where the DSC is  $< 0.4$  or the HD is  $> 2.0$  mm, it is preferable to perform the target alignment without performing bone matching.

In addition, several studies have evaluated breath-holding positional reproducibility using commercially available and in-house DIR software [21–23]. In two studies [21–22], analysis was performed using the deformed vector field (DVF) of the results of the DIR implementation, which is complicated for general users to utilize because a program to analyze the DVF is required. In this study, we used DSC and HD, which are evaluation tools that are attached to the DIR software, based on GTV<sub>CBCT</sub> and GTV<sub>CTS</sub>, which were automatically extracted from the contours of lung tumors by threshold processing. DSC was used to evaluate the similarity between automatic contour extraction, one of the functions of the DIR software, and contouring by radiation oncologists, as well as contour propagation during the acquisition of multiple treatment-planning CT simulator images as the patient's body shape deforms and tumor volume changes [16]. The guidelines state that results with a DSC  $> 0.8$  are in good agreement [16]. In the present study, results with a DSC  $> 0.8$  were also found to be in good agreement with visual assessment. In addition, HD was also used because one type of evaluation method may result in a biased evaluation.

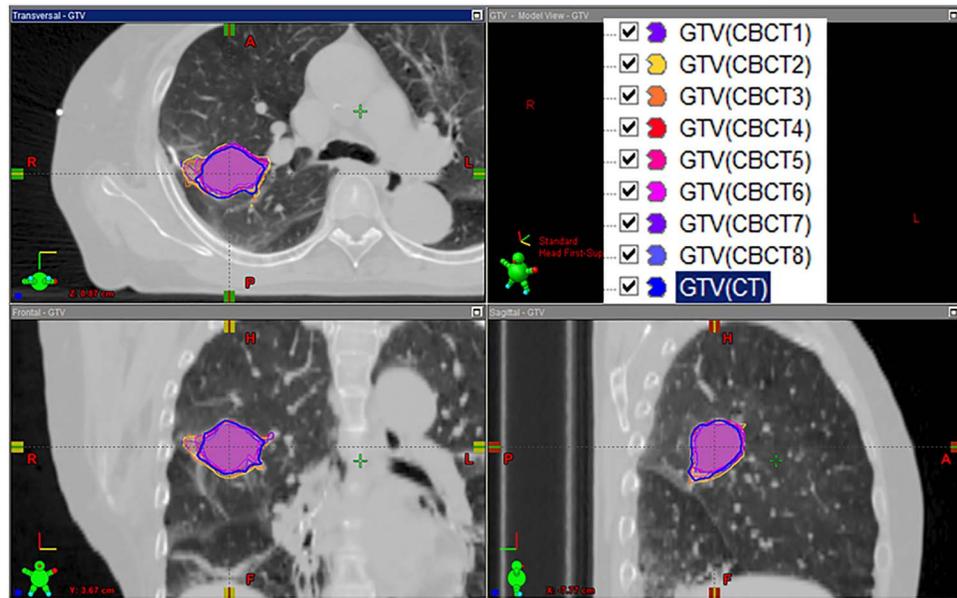


Fig. 5. Contours of  $GTV_{CBCT}$  and  $GTV_{CT}$ s obtained from CBCT taken immediately prior to treatment are shown on Case 1 treatment-planning CT simulator images, which had a DSC > 0.7.

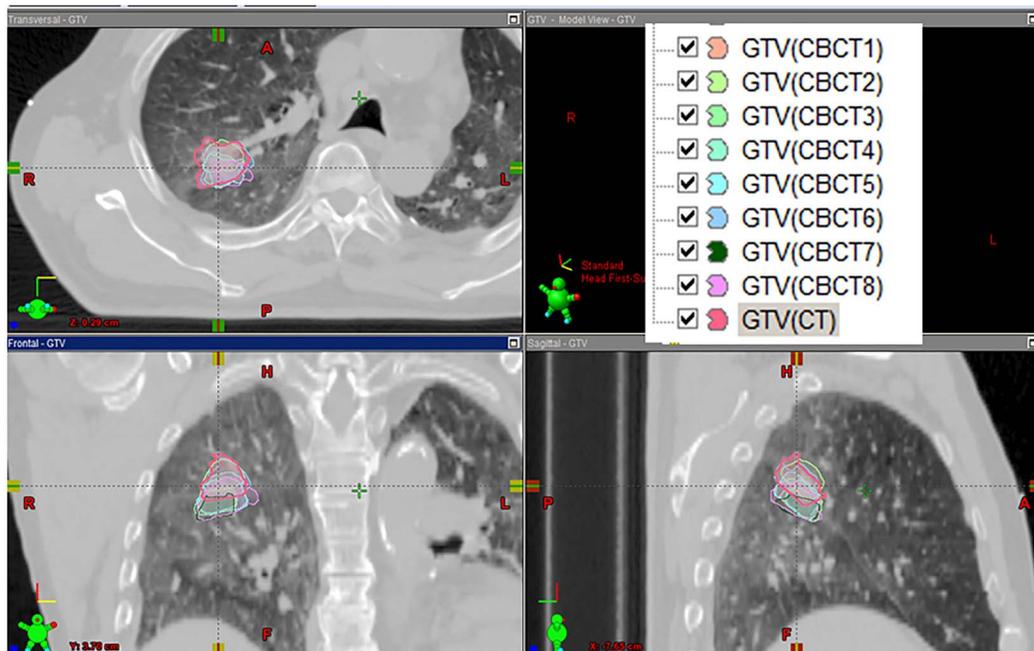


Fig. 6. Contours of  $GTV_{CBCT}$  and  $GTV_{CT}$ s obtained from CBCT taken immediately before treatment are shown on the Case 4 treatment-planning CT simulator image, which had a DSC < 0.5.

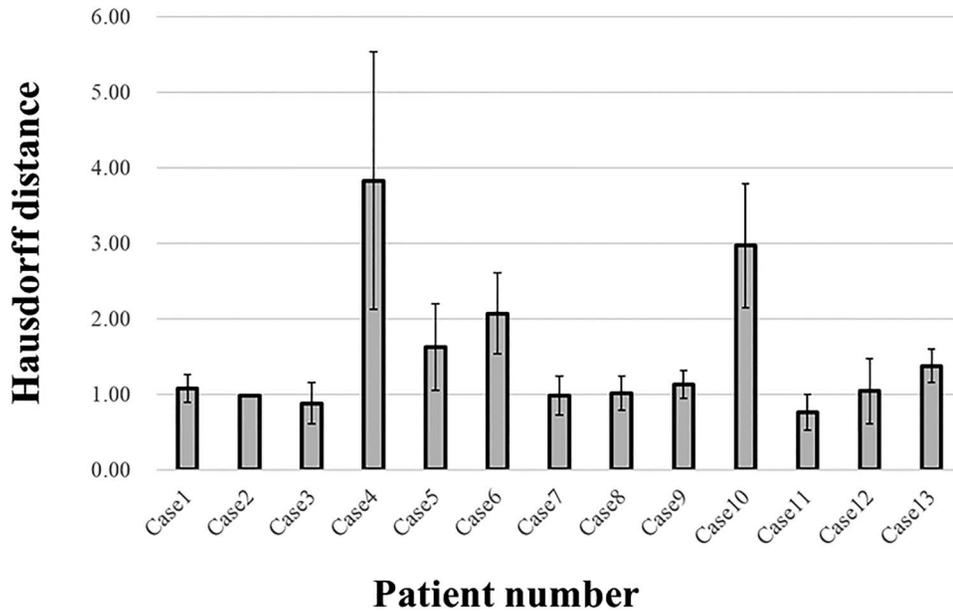


Fig. 7. HD results for GTV<sub>CT</sub> and GTV<sub>CBCT</sub>.

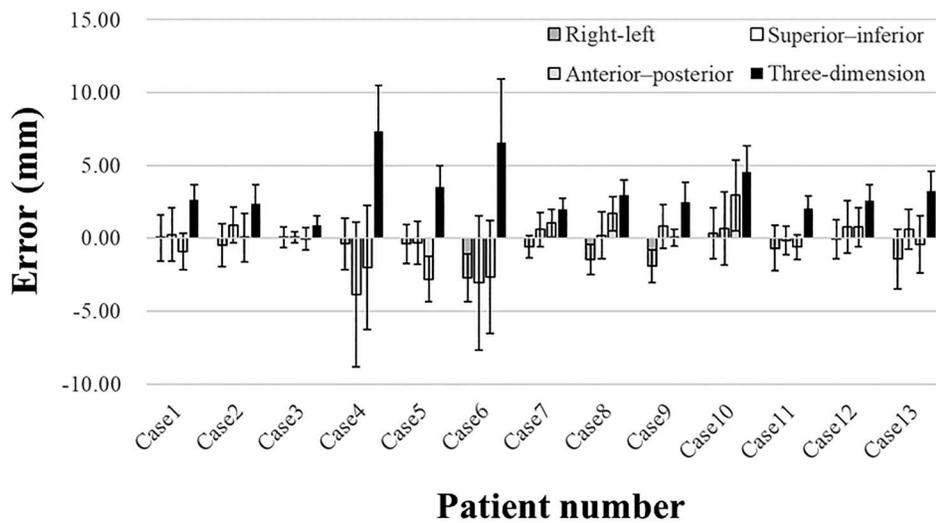


Fig. 8. Results obtained using the conventional feature point method.

When the DSC value is  $\sim 0.7$  and the HD value is within 2 mm, it was found that the breath-hold is reproduced within 5 mm in each direction at the feature points. Alternatively, if the DSC is  $\leq 0.5$  but the HD is  $\geq 2$  mm, it should be noted that the dose distribution may be different from the dose distribution created in the treatment plan when targeted matching was performed. Targeted matching may result in different beam paths, resulting in unintended doses to the organs at risk. In particular, it is necessary to avoid aiming the beam directly above or below the vertebral body in the irradiation field setting. In addition, the DSC may be underestimated when the GTV is small, so it should be evaluated simultaneously with the HD.

In our hospital, when lung cancer is treated with SBRT, the number of fractions is increased to avoid the risk of poor outcomes that might

occur due to the reproducibility of breath-holding between fractions. Since the positional reproducibility of lung tumors in this study is comparable to that reported in previous studies, we are considering reducing the number of fractions in future studies.

It is known that in breath-hold irradiation, a distinction must be made between intra-breath-hold motion, a residual motion that may occur during breath-holding, and intra-fractional organ motion, which occurs during multiple breath-holds without changing the patient's body position [23]. The limitations of the reproducibility of breath-holding in this study have not been evaluated by distinguishing between intra-breath-hold and intra-fractional organ motion.

The proposed method does not require human intervention. We believe that it is possible to perform a simple evaluation regardless

of the maturity level of the DIR software in facilities that uses commercially available DIR software similar to our hospital. In addition, the evaluation of the reproducibility of breath-holding is reasonable based on the results of the present study and previous reports that used conventional feature points. We plan to perform a multicenter study to collect data from many cases where the DSC and HD values are used as guidelines for breath-hold irradiation. It was found that the DSC and HD evaluation methods for the positional reproducibility of breath-hold irradiation, which are proposed in this study, are straightforward and do not require human involvement.

### CONFLICT OF INTEREST

All authors are none declared.

### REFERENCES

- National Cancer Center Information Service. [https://ganjoho.jp/reg\\_stat/statistics/stat/summary.html](https://ganjoho.jp/reg_stat/statistics/stat/summary.html) Last accessed May 30, 2020.
- Nagata Y, Takayama K, Matsuo Y et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–31.
- Onishi H, Shirato H, Nagata Y et al. 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;81:1352–8.
- Nagata Y, Hiraoka M, Shibata T et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan clinical oncology group study JCOG0403. *Int J Radiat Oncol Biol Phys* 2015;93:989–96.
- Ross CS, Hussey DH, Pennington EC et al. Analysis of movement of intrathoracic neoplasms using ultrafast computerized tomography. *Int J Radiat Oncol Biol Phys* 1990;18:671–7.
- Korin HW, Ehman RL, Riederer SJ et al. Respiratory kinematics of the upper abdominal organs: A quantitative study. *Magn Reson Med* 1992;23:172–8.
- Davies SC, Hill AL, Holmes RB et al. Ultrasound quantitation of respiratory organ motion in the upper abdomen. *Br J Radiol* 1994;67:1096–102.
- Nakamura M, Akimoto M, Ono T et al. Interfraction positional variation in pancreatic tumors using daily breath-hold cone-beam computed tomography with visual feedback. *J Appl Clin Med Phys* 2015;16:5123.
- Shirato H, Shimizu S, Kunieda T et al. Physical aspects of a real-time tumor-tracking system for gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;48:1187–95.
- Shiinoki T, Onizuka R, Kawahara D et al. Estimation of patient-specific imaging dose for real-time tumour monitoring in lung patients during respiratory-gated radiotherapy. *Phys Med Biol* 2018;63:065016.
- Pepin EW, Wu H, Zhang Y et al. Correlation and prediction uncertainties in the cyberknife synchrony respiratory tracking system. *Med Phys* 2011;38:4036–44.
- Takamatsu S, Takanaka T, Kumano T et al. Reproducibility of diaphragm position assessed with a voluntary breath-holding device. *Jpn J Radiol* 2013;31:357–63.
- Ueda Y, Takakura T, Ota S et al. Questionnaire survey on treatment planning techniques for lung stereotactic body radiotherapy in Japan. *J Radiat Res* 2020;61:104–16.
- Onishi H, Kawakami H, Marino K et al. A simple respiratory indicator for irradiation during voluntary breath holding: A one-touch device without electronic materials. *Radiology* 2010;255:917–23.
- Kawahara D, Ozawa S, Nakashima T et al. Interfractional diaphragm changes during breath-holding in stereotactic body radiotherapy for liver cancer. *Rep Pract Oncol Radiother* 2018;23:84–90.
- Brock KK, Mutic S, McNutt TR et al. Use of image registration and fusion algorithms and techniques in radiotherapy: Report of the AAPM radiation therapy committee task group no. 132. *Med Phys* 2017;44:e43–76.
- Kim DJ, Murray BR, Halperin R et al. Held-breath self-gating technique for radiotherapy of non-small-cell lung cancer: A feasibility study. *Int J Radiat Oncol Biol Phys* 2001;49:43–9.
- Cheung PC, Sixel KE, Tirona R et al. Reproducibility of lung tumor position and reduction of lung mass within the planning target volume using active breathing control (ABC). *Int J Radiat Oncol Biol Phys* 2003;57:1437–42.
- Mah D, Hanley J, Rosenzweig KE et al. Technical aspects of the deep inspiration breath-hold technique in the treatment of thoracic cancer. *Int J Radiat Oncol Biol Phys* 2000;48:1175–85.
- Japanese Society for Radiation Oncology QA Committee. *Guidelines for Stereotactic Body Radiation Therapy*. <https://www.jastro.or.jp/customer/guideline/2016/10/SRT.pdf> Last accessed Jul 12, 2020.
- Miura H, Ozawa S, Nakao M et al. Evaluation of interbreath-hold lung tumor position reproducibility with vector volume histogram using the breath-hold technique. *Med Dosim* 2020;45:252–5.
- Fukumitsu N, Hayashi Y. Application of a deformable registration technique to investigate breath-hold reproducibility. *Jpn J Radiol* 2014;32:700–7.
- Sarrut D, Boldea V, Ayadi M et al. Nonrigid registration method to assess reproducibility of breath-holding with ABC in lung cancer. *Int J Radiat Oncol Biol Phys* 2005;61:594–607.