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Original Article

Tumor localization accuracy for high-precision radiotherapy during active breath-hold

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ABSTRACT

Background: Conventionally fractionated and stereotactic body radiation therapy (SBRT) for thoracoabdominal tumors may utilize breath-hold techniques. However, there are concerns that differential amounts of inspired airflow may result in unplanned tumor dislocation and underdosing. Thus, we investigated tumor localization accuracy associated with lung volume variations during breath-hold treatment via an automated-gating interface.

Methods: Twelve patients received breath-hold treatment with the active breathing coordinator (ABC) through an automated-gating interface. All breath-hold volumes were recorded at CT simulation, setup imaging, and during treatment, and analyzed as a function of airflow rate into the ABC. The variation of breath-hold volumes was calculated for each fraction over entire course. Intrafraction target motion related to the breathing variation was investigated based on daily imaging acquired before the breath-hold treatment. Correlation between target location and breath-hold variation was statistically analyzed.

Results: The air volume held by the ABC increased as the airflow rate increased on inhalation and decreased on exhalation. The mean range of airflow rate was 0.77 L/s and 0.29 L/s in the conventionally fractionated and SBRT patients, respectively. The maximum air volume difference with respect to the reference volume at the CT simulation was 1.0 L for conventional fractionation and 0.16 L for SBRT. The target dislocation caused by 0.25 L of air volume difference was 6 mm for SBRT. Three patients showed significant correlation between the target location and breath-hold variations.

Conclusions: This investigation shows that because variations in the breath-hold volume may cause target dislocation, patient-specific breath-hold setting is required to improve tumor localization accuracy.

For thoracoabdominal neoplasms, respiratory motion management techniques may improve target control rates by enhancing the accuracy of target dose delivery, and augmenting normal tissue sparing by accommodating tumor motion during the radiotherapy course [1,2]. Treatment planning that accounts for respiratory motion minimizes errors in target and organs-at-risk (OARs) delineation from motion-induced artifacts, which could consequently contribute to reducing the target margin and decrease the treated volume [3].

Tumor motion is identified by imaging of the tumor itself [4], implanted fiducials [5,6], and external surrogates such as markers [7,8], the patient's lung volume, or surface measurements [9,10]. Various techniques to manage respiratory motion, such as breath-hold [1–3,11–17], abdominal compression [18], gating [8,19–23], and tracking [14,24] have been reported. However, with the development of advanced imaging and motion management systems, an evolving issue for modern radiotherapy is automated irradiation triggered by a gating signal synchronized with a mobile tumor.

Using X-ray imaging to track implanted fiducials in or near the tumor is a feasible method to deliver dynamic radiotherapy with high accuracy [22,25–27]. This technique can reduce the size of (or eliminate the need for) the internal target volume, but may prolong the treatment time due to the limited gating window. Other limitations include additional imaging dose to the patient along with operative risks from fiducial implantation [28,29]. Alternatively, an external surrogate has been used to track internal tumor motion and trigger the therapeutic beam [20,30–32]. However, correlation between the external surrogate and internal tumor motion must be verified and periodically checked during the course of treatment. Although tumor motion is assumed to be frozen in breath-hold technique, this is not always the case. The active

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breathing coordinator (ABC; Elekta, Crawley, CA) is a motion management system for holding breath at a predetermined threshold. Despite this fixed threshold, interfraction [33] and intrafraction diaphragmatic motion can still occur [16,17,34]. Moreover, delays in ABC activation, depending on the airflow rate induced into spirometry, can cause variations in lung volume [35].

Since breathing and vital capacities vary among patients, tumor positions could also differ during each breath-hold treatment fraction. As treatment technique becomes more sophisticated by employing advanced motion management systems, uncertainties in the equipment also exist, which could impact the overall treatment quality. The overall geometric uncertainties, especially when multiple pieces of equipment are used, require investigation throughout the course of treatment. Moreover, further scrutiny must be applied when radiation is delivered by automated-gating for high-precision radiotherapy.

The novel objective of this study was to evaluate target positional uncertainties as a function of air volumes and flow, in the setting of both stereotactic body radiation therapy (SBRT) and conventionally fractionated treatment of thoracoabdominal malignancies. In this study, the treatment beam triggered by the predetermined breath-hold setting was automatically delivered through the Response™ gating interface (Elekta, Crawley, CA). During the course of radiotherapy, patients' breath-hold volumes at the time of setup imaging and during treatment were recorded by the ABC, and these volumes were correlated with airflow rates. The actual tumor location associated with the variations in the breath-hold volume was indicated based on the image obtained at the breath-hold.

Methods and materials

Treatment preparation

Under an Institutional Review Board-approved protocol, 12 patients with thoracoabdominal cancers (clinical stage from 0 to IVA) were treated using the breath-hold technique (Table 1). Of these, seven were treated with conventionally fractionated radiotherapy and five with SBRT. The median age of the patients was 64 years, and median Karnofsky's performance status (KPS) was 100. All patients had 1–2 h of breath-hold training prior to CT simulation. Patients were coached regarding breath-holding at inhalation or exhalation until they became familiar and comfortable with the ABC for consistent breath-holds during treatment. Inhalation mode was used for the treatment of tumors in the thorax, whereas exhalation mode was used for the treatment of abdominal tumors. In the training session, the patient's maximum deep breath-hold was measured multiple times and checked until the constant maximum air volume was observed. Then, the breath-hold time was measured by increasing the holding time to the patient's maximum holding time. Once the breath-hold threshold and time were determined, the patient was asked to hold his/her breath multiple times in a row. This training was performed in the supine position until a constant breathing pattern was observed. In the training session, patient-specific breath-hold time and threshold were determined. The breath-hold threshold was defined at 75% of maximum inspiration for lung and breast patients, and at 0.3–0.4 L on end-expiration for liver and pancreas patients. During simulation, patients were scanned with the ABC using the Siemens SOMATOM scanner (Siemens, Germany) using breath-hold techniques. Conventionally fractionated treatment was delivered daily, while SBRT was delivered every other day. The CT scan for treatment planning was obtained using a single breath-hold in all patients, whereas 3 or 4 individual breath-holds were typically required to complete a CBCT scan for patient setup before treatment delivery.

Quality assurance of the ABC device

The ABC system utilizes a spirometer to measure patients' respiratory volumes, which includes a balloon valve, turbine impeller, and opto-electronic sensor (see supplementary Fig. 1) [36]. The balloon valve stops airflow to a patient at a predetermined breath-hold volume. The turbine impeller rotates one revolution for a known air volume. The opto-electronic sensor counts the rotations and detects the airflow signal. During treatment, a function of the spirometric apparatus was routinely checked monthly using a 3-liter (L) spirometer calibration syringe (Vitalograph, Ennis, Ireland). In addition to the routine checks suggested by the manufacturer, we assessed the accuracy of volume measurement by simulating different airflow rates (i.e., 0.5, 1, 1.5, 3 L) into the calibration syringe. Of note, the calibration syringe was manually operated to manipulate the airflow rate. The calibration syringe was calibrated within ±0.5% accuracy of 3 L volume and checked once a year. Of note, the manufacturer recommends performing the air volume measurement at airflow rates of 0.25 L/s and 0.5 L/s to make sure that the measured value is within the tolerance (i.e., 3 L ± 5.0% in accuracy, and 3 L ± 1.5% in consistency) [36].

Data analysis

All patients' air volume was recorded through the ABC during CT simulation and treatment delivery, including daily imaging for setup. The breath-hold volume recorded by the ABC at the time of CT scan was denoted as the reference breath-hold volume in this study. CBCT images were acquired to position the patients in SBRT and volumetric modulated arc therapy (VMAT) with conventional fractionation. Portal images or/and kV images were acquired to

Table 1
Patient and tumor characteristics.

Patient	Gender	Age (y)	Tumor Stage	Tumor Location	KPS
1	F	55	TisN0M0, Stage 0	Lt Breast	90
2	F	61	T2N1M0, Stage IIB	Rt Breast	90
3	F	57	T1bN0M0, Stage IA	Lt CW	100
4	F	64	T1cN1M0, Stage IIA	Lt Breast	100
5	F	79	T1bN0M0, Stage IA	Lt Lung	100
6	F	82	Recurrent, metastatic from low grade endometrial cancer, Stage IVB	Lt Lung	80–90
7	F	63	T1bN0M0, Stage IA	Rt Lung	80
8	M	61	T2N0M0, Stage II	Liver	100
9	M	81	T3N1M0, Stage III	Pancreas	100
10	M	69	T2aN0M0, Stage IB	Lt Lung	90
11	M	58	T4N2M0, Stage IIB	Rt Lung	100
12	F	70	T3N1M1, Stage IVA	Rt Lung	90

Abbreviation: F = female, M = male, KPS = Karnofsky's performance status, CW = chest wall.

position the patients in 3-dimensional conformal therapy (3D CRT) with conventional fractionation. All images were obtained at the predetermined breath-hold setting with the ABC. Once the patient's breathing reached at the breath-hold threshold, then subsequently triggered the therapeutic beam by the Response™ control module. The patient's breathing during the imaging and the treatment was recorded in the output data file at every 20 ms. The actual breath-hold volumes held by the ABC on treatment were compared to the reference breath-hold volume and analyzed as a function of airflow rate. The airflow rate was calculated at the predetermined threshold using MATLAB (R2014a, MathWorks, Natick, MA). The mean breath-hold volume recorded was calculated for each fraction and traced over the entire course of treatment. Additionally, standard deviations (σ) of the breath-hold volumes from each fraction were calculated to analyze the intrafraction variation. Along with the recorded breath-hold volume, the centroid locations of the target relative to the top of the diaphragm in the CBCT images or projection images were statistically analyzed by linear regression using MATLAB. The Pearson correlation coefficient (r) and respective significance (p-value) were calculated to search for linear correlations between the target center and breath-hold volume. Correlations with a p-value <0.05 were considered statistically significant.

Results

A total of 12 patients receiving over 210 fractions in total was treated using the breath-hold technique. Table 2 lists the treatment site, delivery modality, fractionation, patient-specific breath-hold parameters such as breath-hold time and threshold, the reference breath-hold volume obtained from CT simulation, and the maximum difference in air volume measured by the ABC. The air volume was compared with the reference breath-hold volume obtained at the time of CT simulation. Note that patients 8 and 9 performed exhale breath-hold for the treatment in liver and pancreas, respectively, because no dosimetric advantages to the lung and excellent reproducibility in the target location were found in our institution, this has been reported in other studies [37].

The accuracy of the air volume measurement with the ABC was within 5% tolerance, and the consistency was within 1.5% tolerance using a calibrated syringe with 3 L volume, which is suggested by the manufacturer. Fig. 1 shows that the measured air volumes at various airflow rates were within tolerance, but slightly increased as the airflow rate increased. Each dot shows the percent difference of the breath-hold volume recorded in the output data file with respect to 3 L syringe volume at the measured airflow rate. The airflow rate was calculated from the volume difference between the breath-hold volume and end-exhalation right before the breath-hold over time stamp recorded, which corresponds to the gradient at the patient's threshold. Of note, the manual manipulation of airflow rates resulted in different measured results.

Fig. 2 shows the air volumes as a function of airflow rate recorded by the ABC over the entire course of radiation treatment. Each patient displayed different ranges of airflow rate at the time of breath-hold. As a result, the variations in air volume were caused by the variations in airflow rate during breath-hold. Overall, the air volume held by the ABC increased as airflow rate increased. The mean range of airflow rate (i.e., maximum minus minimum airflow rate) was 0.77 L/s for conventionally fractionated patients and 0.29 L/s for SBRT patients. The mean difference of breath-hold volume (i.e., maximum minus minimum air volume) was 0.50 L/s for conventionally fractionated patients and 0.17 L/s for SBRT patients. Variations in the breath-hold volumes were less in SBRT patients as compared to those undergoing conventional fractionation.

Fig. 3 shows the changes in mean and standard deviation of air volume during the course of treatment for each patient. The standard deviation represents the intrafraction variation, which was calculated from all breath-hold volumes in each fraction. In general, patients receiving conventional fractionation showed the largest increase in air volume over the course of treatment. In addition to the increase in the mean air volume, Patient 12 showed the largest interfraction variation. Having too generous of a threshold over the maximum breath-hold may have allowed the expansion of air volume more than expected, leading to the large variations in air volume as exemplified by patients 4 and 12. This variation could be even increased by a fast breathing. Compared to the conventionally fractionated patients, the SBRT patients showed less variations in lung volume per fraction over the whole course of treatment. Patients 5, 8, and 11 showed statistically significant correlation between the centroid location of the target (relative to the top of the diaphragm) and breath-hold volume variations, resulting in the Pearson correlation coefficients r of 0.8 ($p = 0.03$), 0.8 ($p = 0.09$), and 0.7 ($p = 0.0003$), respectively. For patient 8, the top of the diaphragm was directly used to compute the correlation because the target in liver was located close to the diaphragm. Due to insignificant difference in breath-hold volume, Patients 6 and 7 showed no correlation, resulting in $r = 0.2$ ($p = 0.75$) and 0.1 ($p = 0.7$), respectively. Note that no diaphragm in field of view of CBCT for patient 9, and it was difficult to find landmark to analyze the variation in target location for patients 10 and 12 due to changes in target size and shape over treatment.

Table 2
Details of the patient's treatment delivery, predetermined parameters for breath-hold. The reference breath-hold volume indicates the actual air volume held by the ABC during CT simulation. The maximum volume difference was calculated between the reference volume and the maximum (or minimum on inhalation mode) air volume during the treatment.

Patient	Treatment		Breath-hold			Ref. breath-hold vol. (L)	Max vol. Diff. (L)
	Modality	Fx	Mode	Time (s)	Threshold (L)		
1	3DCRT	22	Inhale	30	1.8	1.95	+0.34
2	3DCRT	25	Inhale	25	1.0	1.14	+0.17
3	3DCRT	25	Inhale	25	1.8	1.91	+0.32
4	3DCRT	30	Inhale	25	1.5	1.68	+1.00
5	SBRT	5	Inhale	25	1.4	1.49	+0.09
6	SBRT	5	Inhale	20	1.2	1.29	+0.07
7	SBRT	4	Inhale	20	1.3	1.50	−0.12
8	SBRT	5	Exhale	30	0.3	0.12	+0.16
9	SBRT	5	Exhale	25	0.3	0.17	+0.10
10	VMAT	34	Inhale	25	1.2	1.29	+0.29
11	VMAT	21	Inhale	25	1.2	1.34	−0.13
12	VMAT	30	Inhale	20	1.5	1.78	+0.42

Abbreviation: 3DCRT = 3-dimensional conformal radiotherapy, SBRT = Stereotactic body radiation therapy, VMAT = Volumetric modulated arc therapy, Fx = Fraction, Ref. breath-hold vol. = Reference breath-hold volume, Max vol. Diff. = Maximum volume difference.

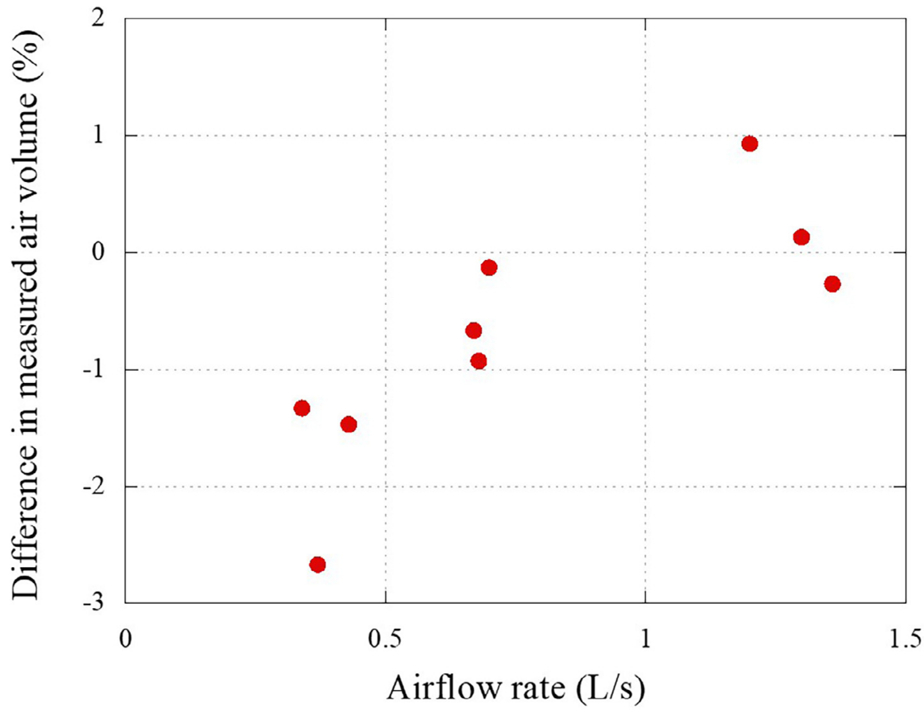

Fig. 1. The difference in the measured air volumes (%) with respect to 3 L reference volume of spirometer calibration syringe as a function of airflow rate.

Fig. 4(a) shows the respiratory curve recorded during 8th fraction (i.e., CBCT scan and irradiation) for patient 11, and Fig. 4(b) shows the tumor in projection images captured at the same gantry angle (−179 degree) and the same breath-hold setting during the CBCT scan. In this fraction, a CBCT scan was repeated due to the patient's irregular respiration during the first scan. Even though the breath-hold threshold remained same at 1.2 L, the patient's respiration was held at the various volumes of 1.26, 1.36, and 1.38 L during the first CBCT scan. Note that since the breath-hold was performed in manual mode on the ABC when a breath-hold volume (1.15 L, 2nd CBCT) was below the threshold, CBCT images were not obtained. As shown in Fig. 4(b), it is obvious that the tumor is at different locations relative to the diaphragm (indicated by the dotted line), which likely resulted from lung volume variations: the left projection was captured at 1.26 L and the right projection was captured at 1.36 L of the breath-hold volume.

Fig. 5 shows two breath-hold CT images of patient 6 captured at the same breath-hold threshold setting (1.2 L). This represents that the degree to which each breath goes beyond threshold can cause target dislocation in treatment. For this patient, the second CT scan was performed to include the patient's total lung volume, as the first CT scan mistakenly did not cover the entire lung for SBRT planning. The recorded air volume was 1.30 L when the CT data set (red) was acquired, and was 1.54 L when the second CT data set (gray) was acquired. The displacement of target location based on the overlaid images was 6 mm in the superior–inferior direction. However, this patient showed insignificant variations in breath-hold volume on CBCT images during treatment. Note that the contour in red indicates the planning target volume drawn by an oncologist on the CT data set at 1.54 L of lung volume.

Discussion

This study reports the novel finding that variations in breath-hold volume, as measured by spirometry, affect target location throughout a course of radiotherapy. We found that all patients showed differences in breathing characteristics such as airflow rate, breath-hold time, and threshold. Because reproducibility using breath-hold platforms for radiotherapy remains a concern, patient-specific breath-hold setting is critical to improve tumor localization accuracy.

Although a constant breath-hold volume is expected throughout the entire treatment with the breath-hold technique using the ABC, variations in air volume were unavoidable because we set the threshold lower at about 75% of the maximum breath-hold as recommended by the manufacturer and others [17,36]. We suggest using tighter thresholds to 90% of the maximum breath-hold to address overshooting above the threshold. Later we observed better reproducibility in several patients who were set at the thresholds to 90% of maximum inhale breath-hold for treatment (See Mendeley Data in Table 3 and Fig. 6). We may even tighten the threshold for patients in normal lung function (KPS score >80 in our case; e.g. Patient 4). However, practitioner still needs to be cautious about tightening too close to the maximum breath-hold in case the patient could not reach the threshold at the time of treatment. Careful decision to the setting should be made considering patient's condition. At consultation (before CT simulation), pre-instruction to the breath-hold technique helps patient understanding during coaching. Moreover, coaching in a soothing manner is crucial to provide a relaxing environment for treatment, because patients' discomfort can cause rapid breaths or complicating breath-holds. With longer treatment times, especially in SBRT, patients may experience discomfort after multiple breath-holds; hence, appropriate coaching is required to maintain the stable breath-hold with comfort.

We found that the breath-hold volume was dependent on the airflow rate. As the airflow rate increased, the breath-hold volume increased beyond the threshold set on inhalation. Despite this, on exhalation, the breath-hold volume decreased as the airflow rate increased; however, these variations were negligible. We suggest that volume measurements with the ABC should be ensured at a wide range of airflow rates, rather than performing QA only at two airflow rates as suggested by the manufacturer. The variations dependent on the airflow rate were less for patients receiving SBRT

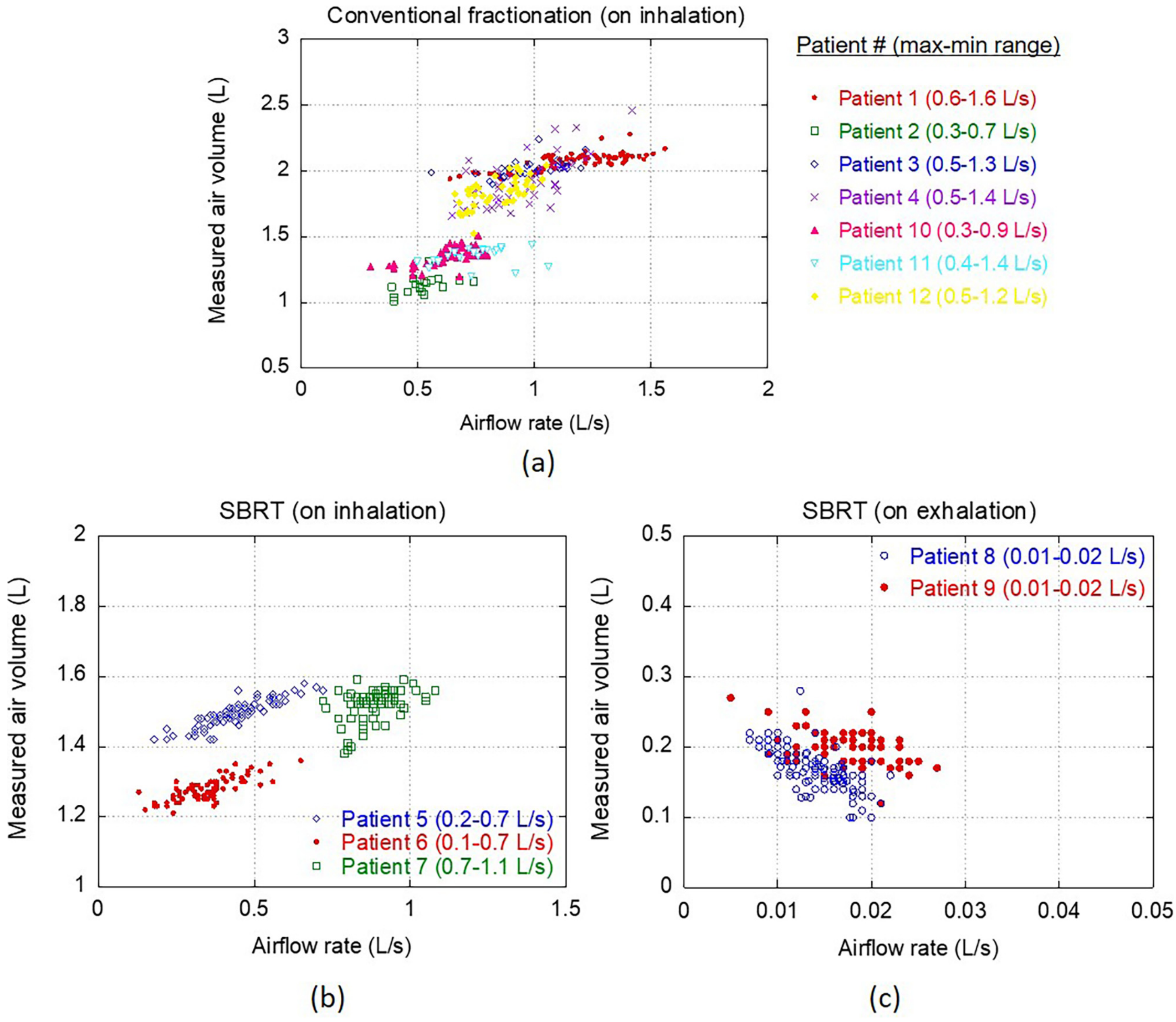

Fig. 2. The air volume measured by the ABC as a function of airflow rate. (a) Patients receiving conventionally fractionated treatment on exhalation mode, (b) patients receiving SBRT on inhalation, and (c) patients receiving SBRT on exhalation.

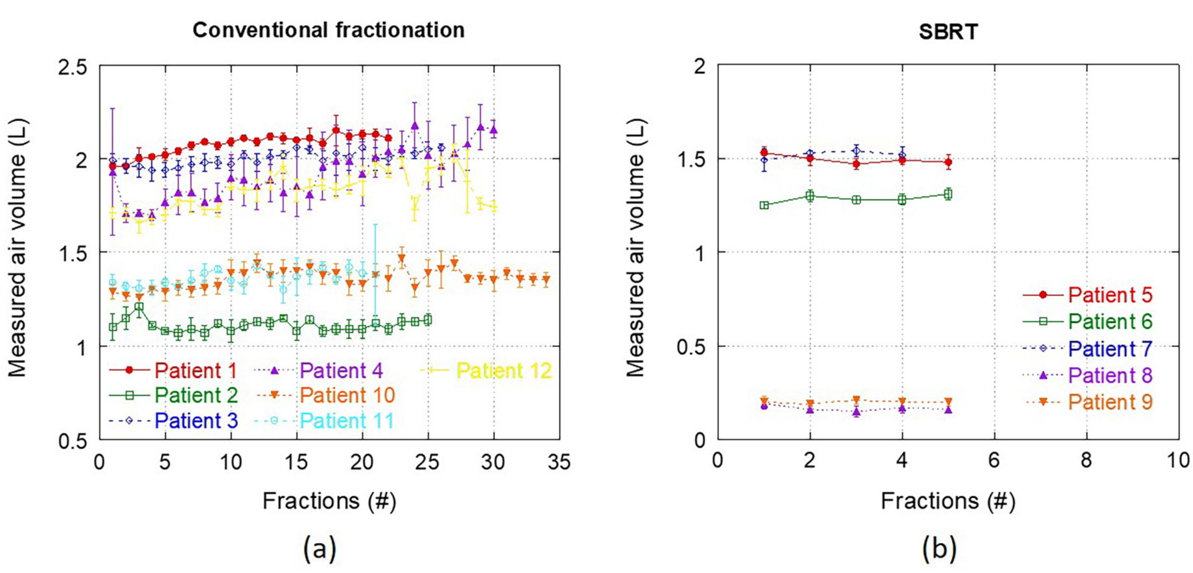

Fig. 3. The mean and standard deviation of the measured air volume per fraction during the course of treatment for each patient. (a) Patients receiving conventional fractionation, and (b) patients receiving SBRT.

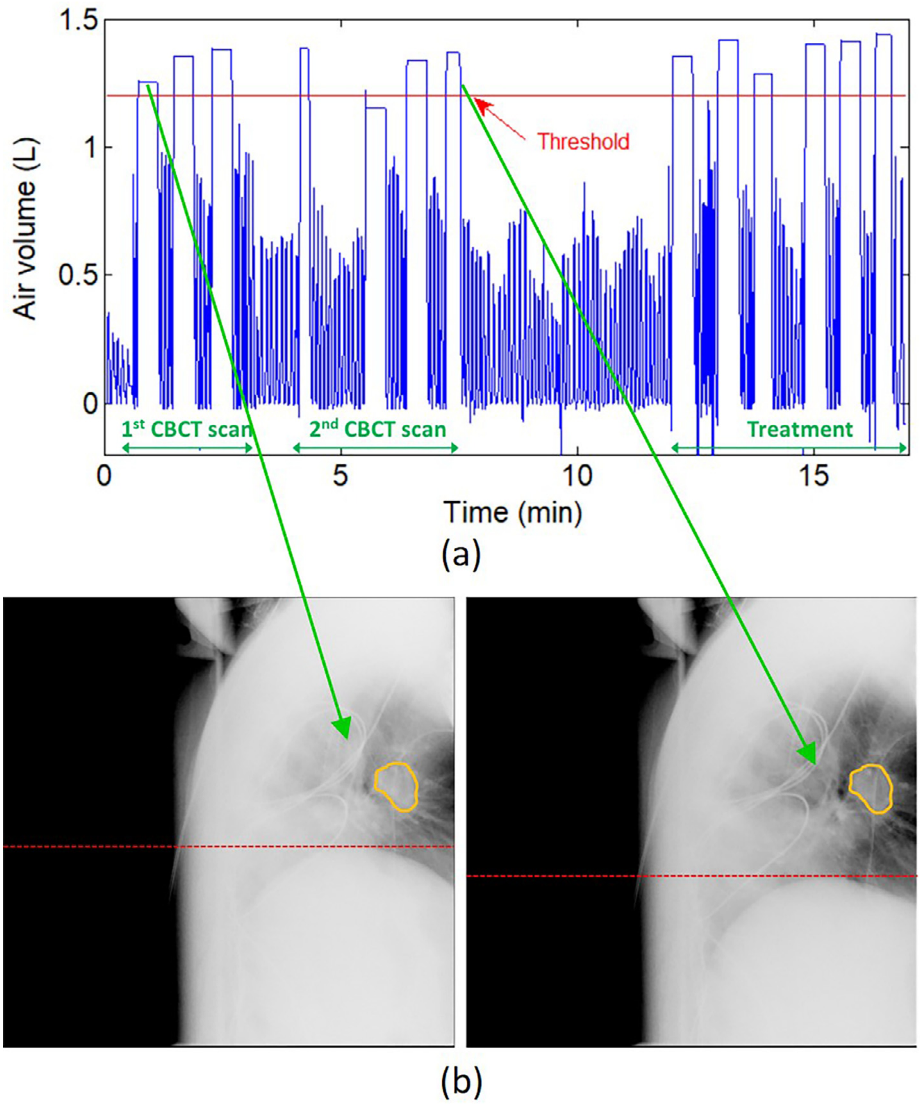

Fig. 4. (a) The respiratory curve of patient 11 recorded in the ABC output data file during the treatment including two subsequent CBCT scans. The solid red line indicates the predetermined threshold (1.2 L) for the breath-hold. Breath beyond the threshold will trigger the machine to deliver radiation treatments. (b) The projection images captured at the corresponding breath-hold during the CBCT scans. The tumor was in a different location relative to the diaphragm (indicated as dotted red line). The left projection (window level: 64477, width: 2116) was captured at 1.26 L and the right projection (window level: 64492, width: 2085) was captured at 1.36 L of breath-hold volume.

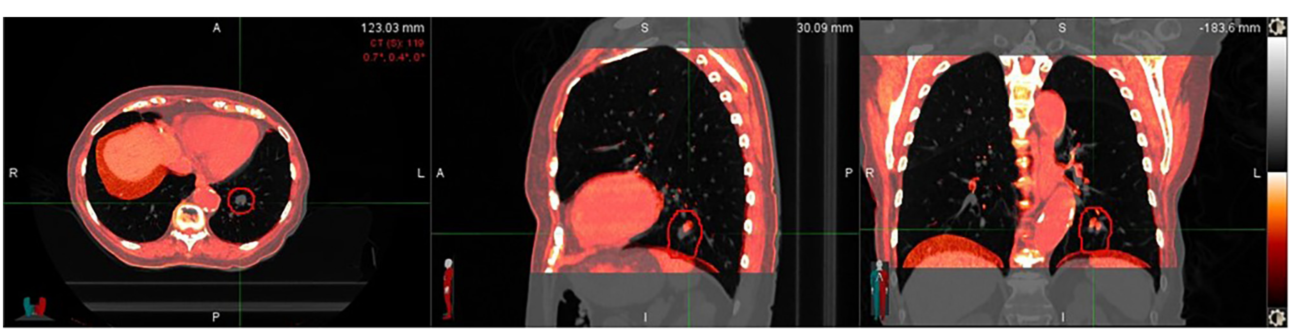

Fig. 5. Two CT images acquired at the same threshold (1.2 L). The recorded air volume was 1.30 L (red) and 1.54 L (gray), respectively.

as compared to those patients receiving conventional fractionation. Also, each breath-hold mode (i.e., inhalation for lung and exhalation for abdominal tumor) produced the excellent reproducibility in breath-hold volume during treatment ($\sigma < 0.01$ L). The following factors may explain these findings. (1) SBRT was completed within 10 days, which was shorter than the conventional fractionation. The number of breath-holds in the short period was less in SBRT (in our case, 84 breath-holds on average in SBRT vs. 328 breath-holds on average in regular fractionation), and hence, may result in less variation in the breath-hold volume. (2) The tighter threshold to the patient's maximum breath-hold may be applied for SBRT. Additionally, (3) the SBRT patients may have less tumor burden. For the patients receiving conventional fractionation, the measured air volume increased over the treatment course. The possible reasons were that (1) patients became familiarized and comfortable with the ABC as treatment progressed. (2) Patients may have improved their breathing capability over the course of treatment, leading to their increased capacity to maintain a constant lung volume. Three patients (patient 5, 8, and 11) indicated statistical correlations between the breath-hold variations and the target locations based on the Pearson correlation coefficient. In the correlation computation for patient 8, only 5 CBCT image sets were included for statistical analysis because some CBCT images were excluded due to low image quality. In this study, the target location relative to diaphragm was used for correlation analysis since target may remain in same location even though the diaphragm position or shape is different, which depends on the target location or patient's anatomy.

This study only addressed the variation in intrafraction motion at breath-hold, since the interfraction motion was removed using daily image guidance. The variations in interfraction motion may not significantly impact dose deviations to the target or normal tissues [6,38], particularly in 3D breast treatment when image guidance is utilized [17]. In this study, we detected the couch shift in vertical direction associated with the breath-hold volume changes in patient 4: 3.1 cm and 1.5 cm couch shift to posterior with respective to the couch position in fraction 1st was recorded in fractions 4th and 14th due to +0.26 L and +0.15 L of breath-hold volume difference, respectively. We found no significant couch shift for treatment in other 3D patients in this study. The excellent target reproducibility using kV and MV images and acceptable interfraction variability at breath-hold has been reported in many other studies [39]. However, the dose deviation to OARs could be more pronounced with VMAT techniques in patients with large breathing variations. Thus, the tumor location when imaging is performed should be consistent with the tumor location when the therapeutic dose is delivered. Therefore, one should exercise caution when a measured air volume is far beyond the threshold, or when the difference between the air volume at imaging and at irradiation is significant. This is critical when the treatment delivery is automated through the gating interface.

Our study showed that a breath-hold technique using the ABC could be effective to minimize the intrafractional breathing variation during treatment, especially for SBRT. Ge et al. found significantly large intrafractional breathing variations in patients with abdominal tumors treated with SBRT as compared to conventional fractionation based on daily fluoroscopy [6]. Velec et al. investigated that, for liver SBRT, the intrafractional tumor motion resulted in dose deviations up to 22% relative to the planned dose [38]. Without motion management, the intrafractional motion variation could result in dose deviation from the planned dose due to breathing variability, especially in the setting of SBRT. In this study, the variations in intrafraction motion were less in SBRT patients when using the ABC. However, the breath-hold parameters depending on patients' breathing characteristics should be meticulously examined before treatment. Even though the patient population was limited by the small sample sizes, the difference is obvious between the SBRT and the conventionally fractionated patients. However, it is also worth to consider other factors (e.g., lung function related to individual smoking history (or lack thereof), chest wall compliance and shape) that could influence breath-hold volume. Another limitation of this study is that dose deviation was not investigated when target dislocation was observed. Further investigation of dosimetric correlation with the breath-hold technique will contribute to accurate treatment for automatic treatment in radiotherapy.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.036.

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