air-injected blanket has also been suggested for abdomen compression and fixation (10) to reduce breathing-induced organ motion.

In this study, we evaluated the effectiveness of a body frame and its combination with a diaphragm press in restricting the range of lung tumor motion by tracking the three-dimensional real-time position of fiducial gold markers embedded near the tumor. We also investigated the effect on respiratory-induced organ motion of using the stereotactic body frame (SBF) together with a breathing cycle monitoring device (Abches), which was used to self-regulate the patient's breathing cycle.

MATERIALS AND METHODS

The real-time tumor-tracking radiotherapy system

The three-dimensional trajectories of fiducial markers near or at tumor sites were tracked via the real-time tumor-tracking radiotherapy (RTRT) system at the Radiotherapy Department of Hokkaido University Hospital (5, 6, 11, 12). This fluoroscopy-based system is composed of two pairs of an X-ray source and image intensifier and an image acquisition and recognition unit that is interfaced with a linear accelerator to perform gated-irradiation. The positions of the gold markers were acquired every 0.033 s.

Body frame, diaphragm press, and breathing cycle monitor

For patient immobilization, we used Elekta's SBF (Elekta Oncology Systems) (13, 14). The same body frame was used in an earlier investigation on respiratory tumor movement and setup error verification using X-ray simulator images (7, 9, 15). The SBF is made from a rigid material formed into a half-hexagonal shell that wraps around the patient's torso. Because of the restricted space inside the shell, the patient's arms had to be positioned outside the shell by raising them above the head. Patient fixation inside the body frame was accomplished by means of a vacuum pillow, the size of which was chosen to ensure that it could provide an exact fit to the patient's body contour.

An additional accessory to the SBF was a frame that supports a pentagonal plastic plate that can be placed against the patient's abdomen to restrict the diaphragm motion. The pressure applied by the plate was regulated depending on the tolerance of each patient and was used only in the part of our measurements where its effectiveness to control motion from respiration was evaluated.

A breathing cycle monitor (commercially available as Abches [APEX Medical Inc., Tokyo, Japan]) was also used in combination with the body frame to investigate whether self-regulated breathing can reduce the amplitude of respiratory-induced tumor and organ motion. As shown in Fig. 1, the Abches consists of two extended arms, one for detecting abdominal movement and the other for detecting chest movement, and a respiration range indicator visible to the patient through a mirror attached to the head during the measurement.

Patient demographics

The patient population for this study was composed of 16 males and 3 females who were scheduled to undergo radiation therapy using the RTRT system in our hospital between 2006 and 2008. Table 1 shows the characteristics of the cohort for this study. The patients' ages ranged between 59 and 85 years (mean, 76 years). Fourteen patients had T1 lung cancer, whereas 5 had T2 and 1 had T3. No patient had lymph nodes irradiation and none of the patients had metastasis. Four patients had partial lung resection before the irradiation.

Table 1. Characteristics of the cohort for this study

Parameters	Number of patients
Sex	
Male	16
Female	3
Age range	59–85 (mean, 76)
Gold marker locations	
Upper right lobe	5
Middle lobe	1
Lower right lobe	4
Upper left lobe	6
Lower left lobe	3
Cancer classification	
T1N0M0	13
T2N0M0	5
T3N0M0	1

The locations of the gold markers were judged based on where they appeared in the computed tomography images of the patient. We classified the sample population into "upper lobe" or "middle or lower lobe" patients according to the location of gold markers in the lungs, because it has been reported that the relative locations in

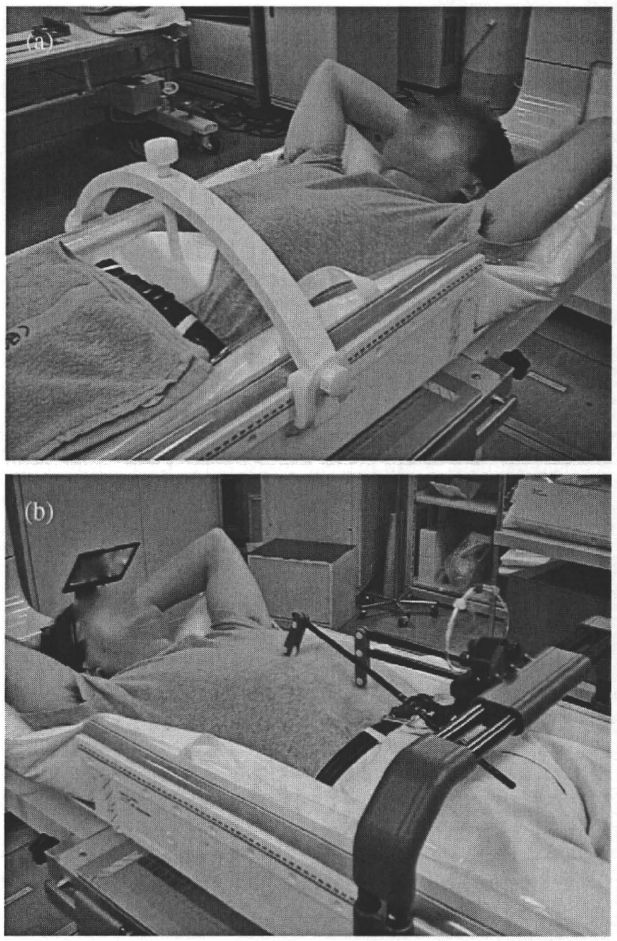

Fig. 1. Patient set-ups using the (a) stereotactic body frame (SBF)+diaphragm press (left) and the (b) SBF + Abches (right).

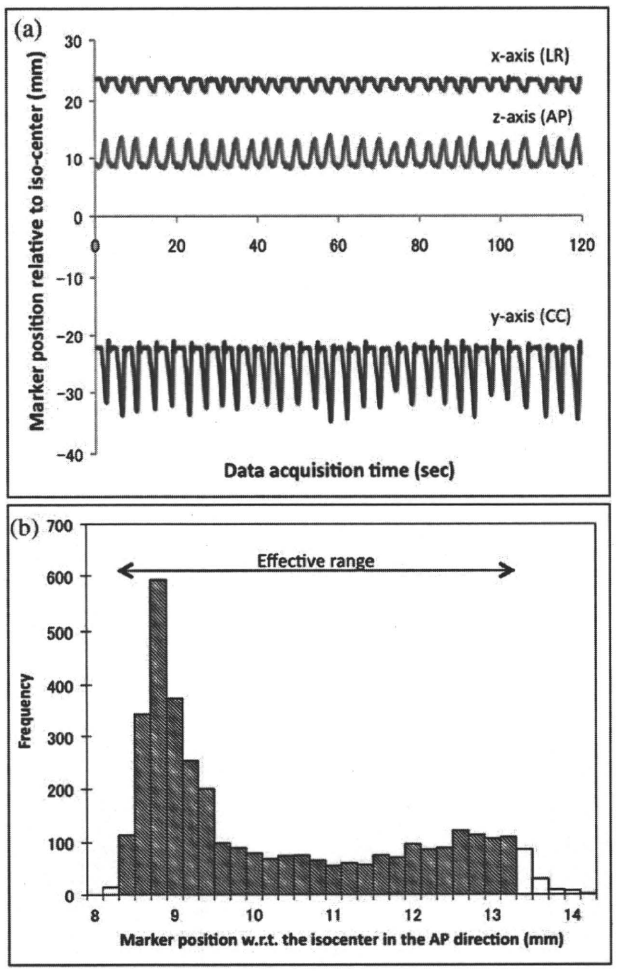

Fig. 2. Shown in (a) is an example of a 2-min tracking of the data from which the effective range was computed. The effective range along the z axis of the data in (a) is shown in (b).

the lung of the gold marker (16) and the tumor itself (17) influence the amplitude of their respective motions. Eleven of the 19 patients who participated in this study had gold markers embedded in the upper lobes of their lungs: 6 of the 11 had markers in the upper left and the other 5 had markers in the upper right. There was 1 patient with markers in the middle lobe and 7 patients with markers in either the lower left or lower right lobes of the lung.

Patient setup

Fluoroscopic tracking of the fiducial markers was performed in five different setups for each patient. In the first setup, the patient was made to lie on the treatment couch in the supine position with arms on the side. This was set as the reference patient position. In the second setup, the patient's arms were placed overhead to mimic the patient position when an SBF is used. The arms were not fixed into any structures, but were supported by cushions for patient comfort. The patient was asked to lie in the SBF in the third setup. Figure 1a shows the fourth setup, in which respiration was restricted using a plastic plate that pressed against the patient's diaphragm. In the fifth setup, shown in Fig. 1b, the Abches was attached to the SBF in the same manner as the abdominal press. The patients were able to monitor the relative amplitude of their breathing cycle from a respiration range indicator which was visible to the patient through a mirror.

Marker tracking

Tumor motion was monitored in real time by using 2-mm diameter gold markers, which were surgically placed near the tumor site and served as surrogate indicators of lung tumor motion (4). Three tracking measurements lasting for 5 min (2 min of tracking plus 3 min of rest) each were performed for every patient setup. The range of patient dose for the entire duration of marker tracking was between 14 and 591 mGy based on the estimates of Shirato *et al.* (18). Because the absorbed dose in the patient is strongly dependent on the tube voltage and pulse width, the X-ray tube settings were kept as low as possible during all the measurements.

Evaluation index and statistical analysis

The three-dimensional position of the gold marker relative to the iso-center is estimated by the RTRT system as it tracks the marker's motion. Sample tracking data are shown in Fig. 2a. The *effective range* of marker motion along each coordinate axis was computed about the mean marker position from the respective 2-min set of tracking data. Histograms similar to Fig. 2b with 0.2-mm position bins were constructed for each coordinate axis. The frequencies of the adjacent bins to the left and to the right of the median were accumulated until 95% of the total marker position frequency was achieved. The range of the included position bins was then defined as the *effective range* of the marker motion. The effective range along the z axis of the data in Fig. 2a is given as an example in Fig. 2b. A smaller effective range of the gold marker indicates less respiratory-induced organ motion.

The Mann-Whitney test was applied to assess the statistical significance of the differences in the effective ranges obtained between the reference setup and the other four setups.

This study was thoroughly discussed with the institutional review board of our hospital and its approval was received before the commencement of the measurements. Written patient consent was also received from all the participants in this research.

RESULTS

The effective ranges were observed to vary from patient to patient. In the reference setup (no SBF-arms down setup), the range was 0.60–5.27 mm, 0.93–19.93 mm, and 1.00–10.20 mm along the left-right (LR), craniocaudal (CC), and anteroposterior (AP) directions, respectively, among the 19 patients. The tumor motion, as indicated by the effective range of the tracked gold marker, was reduced in some patients by changing the patient setup, such as by placing the patient's arms overhead or by using the SBF and diaphragm press or Abches. However, this was not true for all the patients, because there were those whose range of tumor motion became worse in the setups other than the reference setup. Because of the small number of patients, we grouped the tumors into two categories: upper lobe and middle or lower lobe. In the reference setup, the CC direction yielded a significant difference in the mean effective range of the upper and middle or lower lobe markers, with a p value of 0.02. On the other hand, the differences in the mean effective range of markers in the upper lobe and the middle or lower lobes were not statistically significant for either the LR or AP direction in the reference setup.

We compared the effectiveness of each setup in reducing respiratory-induced intrafractional organ motion. Table 2

Table 2. Comparison between the mean effective ranges of motion (±1 SD) of the markers in the upper and middle or lower lobes for the 5 patient setups evaluated

		LR	CC	AP
No SBF, arms down (nSBF_AD)	Upper	2.15 ± 0.89 (0.60–3.20)	4.59 ± 3.01 (0.93–9.53)	3.39 ± 1.42 (1.00–5.87)
	Middle or lower	2.18 ± 1.60 (0.60–5.27)	10.93 ± 6.36 (1.07–19.93)	4.33 ± 3.05 (1.13–10.20)
	p value	0.66	0.02	0.72
No SBF, arms up (nSBF_AU)	Upper	2.21 ± 0.96 (0.67–3.73)	4.51 ± 3.06 (0.87–10.13)	3.23 ± 1.63 (1.00–6.27)
	Middle or lower	2.55 ± 1.56 (0.67–5.60)	10.6 ± 6.09 (1.07–19.00)	3.91 ± 2.45 (1.33–8.27)
	p value	0.72	0.03	0.72
With SBF (wSBF)	Upper	1.97 ± 0.89 (0.67–3.33)	4.23 ± 2.76 (0.67–9.53)	3.04 ± 1.54 (1.07–5.67)
	Middle or lower	2.98 ± 2.41 (0.87–6.93)	9.91 ± 5.67 (1.07–16.87)	4.43 ± 3.63 (0.93–10.60)
	p value	0.78	0.03	0.84
With SBF + diaphragm press (wSBF + DP)	Upper	1.95 ± 0.86 (0.60–3.33)	3.77 ± 2.57 (0.80–8.60)	3.09 ± 1.33 (1.20–5.27)
	Middle or lower	2.53 ± 2.23 (0.73–7.60)	9.43 ± 5.56 (0.80–16.33)	3.61 ± 2.64 (0.67–8.93)
	p value	0.90	0.03	0.97
With SBF + Abches (wSBF + Ac)	Upper	1.91 ± 0.81 (0.60–2.93)	3.98 ± 2.68 (0.73–8.33)	2.88 ± 1.23 (1.20–4.60)
	Middle or lower	3.27 ± 2.70 (0.67–7.73)	12.84 ± 6.37 (1.00–18.87)	5.04 ± 4.81 (0.93–13.40)
	p value	0.89	0.01	0.60

Abbreviations: LR = left-right; AP = anteroposterior; CC = craniocaudal; SBF = stereotactic body frame.
Given in brackets are the minimum and maximum effective ranges. The *p* values listed here are derived from the Mann-Whitney test.

shows the mean effective ranges of marker motion for all the patients in the five setups evaluated in this study. Also listed in Table 2 are the *p* values obtained from the nonparametric comparison of the mean effective marker range between the upper and the middle or lower groups of patients for each setup using the Mann-Whitney test. Measurements using these setups were carried out for all the patients except for 2 patients who decided not to continue with the measurements after the fourth setup. The sequences of setups for the tracking sessions were randomly changed between patients to minimize the possible bias from the setup sequence. Results of the RTRT measurement of the effective range of motion of fiducial markers showed that the use of the SBF, diaphragm press, or breathing cycle monitor to control the patient's breathing did not generally yield smaller effective marker ranges either for tumors in the upper lobe or those in the middle or lower lobes.

Motion of markers in the upper lobe

The mean effective ranges in the LR direction of the markers in the upper lobe showed little variation among the different patient setups. In the LR direction, they were around 2 mm for all setups (Fig. 3). The differences between the reference setup and the four other setups were no more than 1 mm, and none of these differences were statistically significant at the 5% level. Along the CC direction, the average effective ranges of the markers in the 5 setups were between 3.77 mm and 4.59 mm (Fig. 4). The mean and median of the effective range were around 2.88 mm to

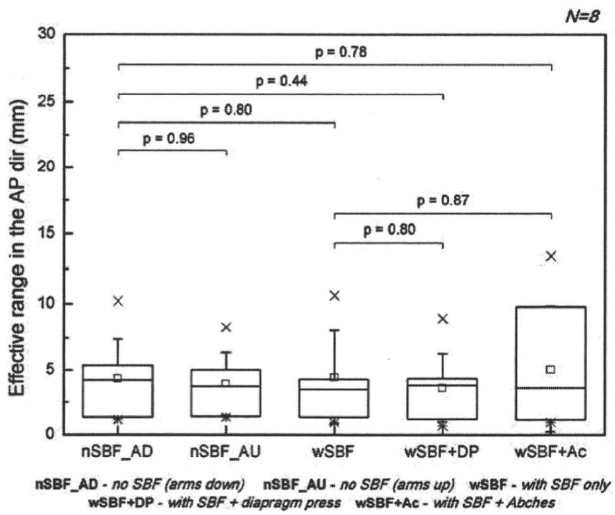

Fig. 3. The effective range along the lateral direction of the gold markers in the upper lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

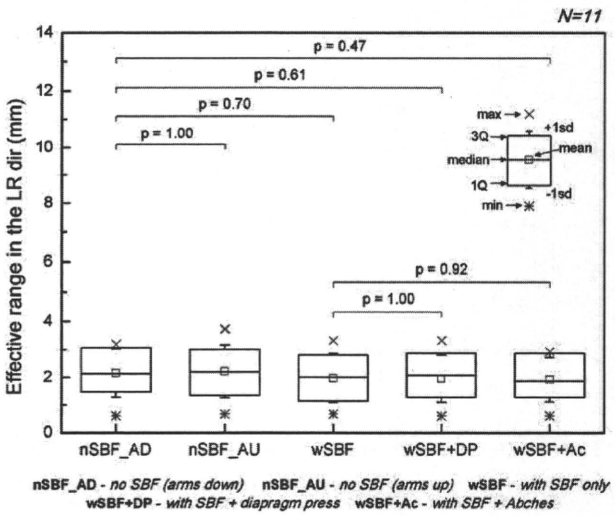

Fig. 4. The effective range along the craniocaudal direction of the gold markers in the upper lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

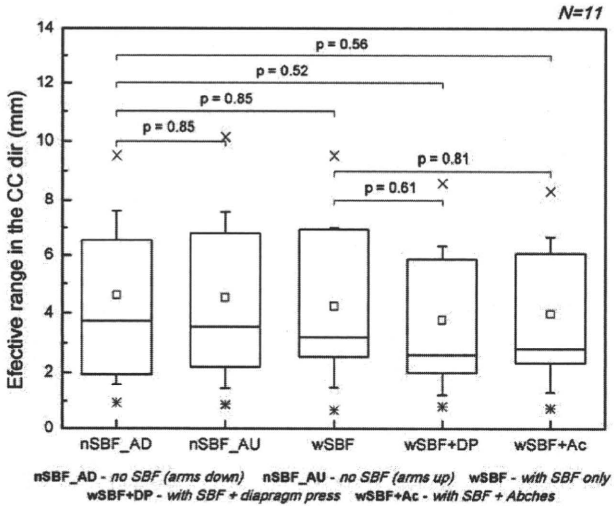

Fig. 5. The effective range along the anteroposterior direction of the gold markers in the upper lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

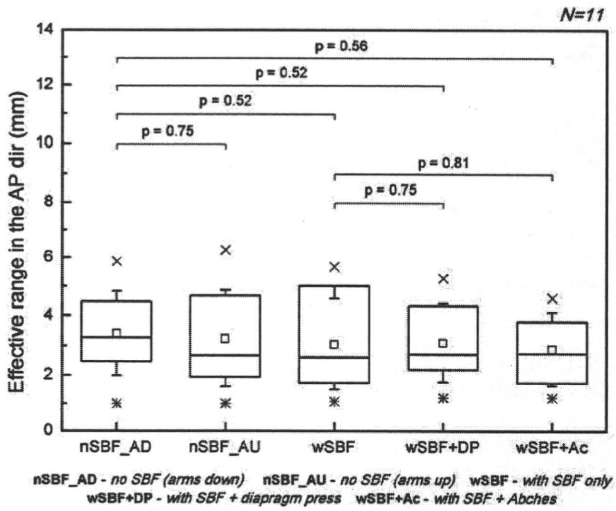

Fig. 6. The effective range along the lateral direction of the gold markers in the middle or lower lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

3.39 mm in the AP direction (Fig. 5). The spread of the effective range values was largest along the CC direction, with a standard deviation of about 2.57–3.06 mm, and smallest along the LR direction, with a standard deviation of less than 1 mm. The maximum effective ranges of the markers obtained from the LR, CC, and AP directions were 3.73 mm, 10.13 mm, and 6.27 mm, respectively.

Motion of markers in the middle or lower lobes

As shown in Fig. 6, a slight variation in the mean effective range along the LR direction for the five setups was observed in the middle or lower lobe markers, with values between 2.18 mm and 2.98 mm; however, these differences were also not statistically significant (see The *p* values in Fig. 6).

The spread of the effective ranges for this group was greater than that for the upper lobe markers, which had standard deviations of 1.56–2.70 mm.

Shown in Fig. 7 are the effective ranges in the CC direction for the middle or lower lobe markers. Although the two setups without SBF had mean effective ranges greater than 10 mm and the mean effective ranges for the SBF setup and the SBF + diaphragm setup were less than 10 mm, the differences in the mean effective range between the setups were not statistically significant. The use of the Abches for this group of patients resulted in a mean effective range of about 13 mm. The standard deviations of the effective ranges in the CC direction were between 5.56 mm and 6.37 mm.

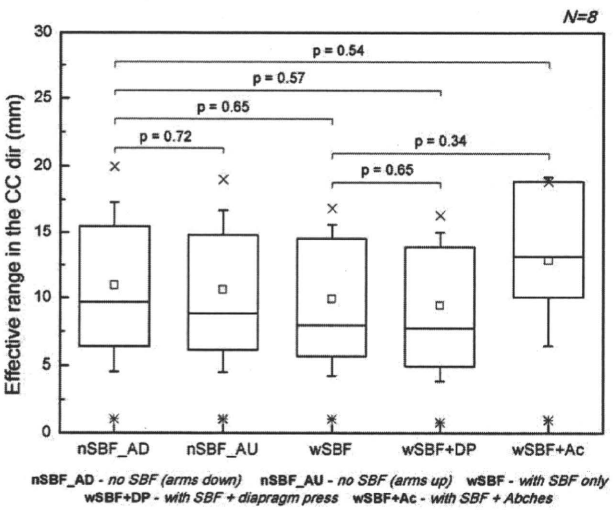

Fig. 7. The effective range along the craniocaudal direction of the gold markers in the middle or lower lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

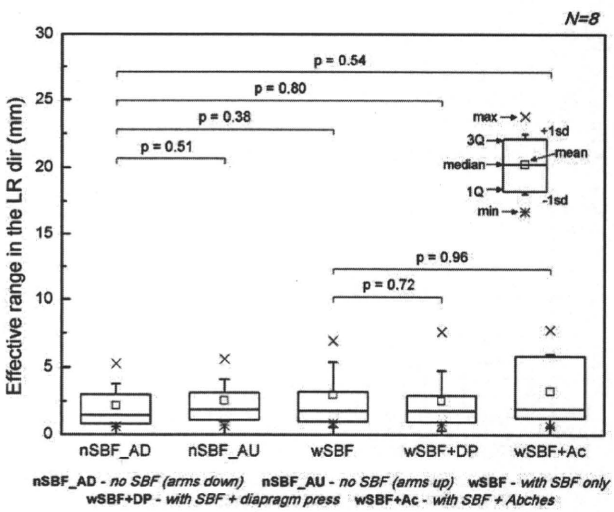

Fig. 8. The effective range along the anterior-posterior direction of the gold markers in the middle or lower lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

The effective ranges in the AP direction for the middle or lower lobe markers were also greater than their upper lobe counterparts. The mean effective ranges shown in Fig. 8 for the five patient setups are between 3.61 mm and 5.04 mm with standard deviations between 2.45 mm and 4.81 mm. Again, no significant differences were noted among the five setups. The setup including the Abches had the largest mean effective range of 5.04 ± 4.81 mm.

DISCUSSION

In the present study, the real-time tracking capability of our RTRT system was used to determine the three-dimensional motion of fiducial gold markers embedded near or at the tumor to determine whether the respiration-induced motion of these markers can be controlled in free and restricted breathing setups. With the RTRT system, we were able to determine the instantaneous displacement of fiducial markers near the tumor, as has been done in previous studies (7, 15, 19, 20), as well as the full range of motion of these markers. This allowed a more comprehensive evaluation of the feasibility of controlling respiratory-induced motion by using an SBF, diaphragm press and breathing cycle monitor.

The motions of fiducial markers were found to be highly patient-dependent and were influenced by the location where the markers were embedded in the lung. In general, markers in the upper lobes exhibited a smaller range of motions along the LR, CC, and AP directions compared with the motions of the markers in the lower lobes, which are consistent with the previous results reported by Seppenwoolde *et al.* (3) and Onimaru *et al.* (16). The average effective ranges of marker motion in the present study were comparable with the amplitudes obtained in the three-dimensional analysis by Seppenwoolde *et al.* (3) of tumor motion in the lung in a setup without SBF and with the patient's arms down.

The markers in the upper lobe of the lung exhibited ranges of motions, which did not vary significantly irrespective of the patient setup used. Additionally, their maximum effective ranges, which were all observed in the CC direction, were <10 mm. Engelsmann *et al.* (21) have previously reported that respiration-induced tumor motion of up to 10 mm does not drastically change the dose distribution. Thus, the patient breathing control may no longer be necessary for the majority of tumors in the upper lobes of the lung.

The markers in the middle or lower lobes of the lung exhibited larger motion in the CC direction and larger spread in the individual effective ranges in the LR, CC, and AP directions. Thus, respiration-induced tumor motion management for tumors in the lower lobes is worth considering, if possible (21).

We evaluated five patient setups in this study with the goal of reducing respiration-induced tumor motion; however, we found that the effective range of marker motions in the lower lobes of the lung was not significantly different among these setups. This result is different from the pioneering studies of Lax *et al.* (7) and Negoro *et al.* (9), which attempted to limit the abdominal motion of patients using the SBF and a diaphragm press. However, the comparisons between setups with or without a diaphragm press in the two aforementioned studies were done with a smaller number of patients compared with the present study (7, 8). Lax *et al.* noted that the diaphragmatic motion was reduced from a range of 1.5–2.5 cm to a range of 0.5–1.0 cm in 17 patients evaluated using fluoroscopy (7). Negoro *et al.* found that tumor motion in the CC direction was reduced from 8–20 mm for the setup with SBF down to only 2–10 mm for the setup using SBF and diaphragm press in 10 patients (9). However, they also had 1 patient whose tumor movement of 7 mm increased to 10 mm upon the use of diaphragm control. Compared with the previous visual measurement using AP fluoroscopy, the present study measured the three-dimensional motion of the internal fiducial markers with more objective and reproducible methods. Thus the discrepancy in the results between these pioneering works and the present study may have been related to the methods used or the precision of the measurements, together with other factors such as the patient background (*e.g.*, tumor stage, location of tumors).

Additionally, although the tracking sessions were performed using a random sequence of patient setups, this may not have completely eliminated some bias due to patient setup, since by the time the patient goes through the last setup, he or she would have been on the couch for at least 20 min longer compared with the first setup. We also cannot neglect the possibility that some patients might have benefited from any of the setups evaluated in this study because of the relatively small patient population. However, it is not possible from our study to recommend the use of the SBF alone or in combination with the diaphragm press or the Abches as a universally effective method to control respiratory intrafractional organ motion.

In conclusion, our RTRT measurement of the effective range of motion of fiducial markers showed that using the SBF, the diaphragm press, or a breathing cycle monitor for the purpose of controlling the patient breathing does not generally result in smaller effective marker ranges. Whether these patient setups will be effective in reducing respiratory-induced organ motion should be examined for individual patients before using them in the radiotherapy.

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REPORT

PHASE II STUDY OF CHEMORADIOTHERAPY WITH 5-FLUOROURACIL AND CISPLATIN FOR STAGE II–III ESOPHAGEAL SQUAMOUS CELL CARCINOMA: JCOG TRIAL (JCOG 9906)

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Purpose: In this Phase II study, we evaluated the efficacy and toxicity of chemoradiotherapy (CRT) with cisplatin (CDDP) and 5-fluorouracil (5-FU) for Stage II–III esophageal squamous cell carcinoma (ESCC).
Patients and Methods: Patients with clinical Stage II–III (T1N1M0 or T2–3N0–1M0) thoracic ESCC were enrolled between April 2000 and March 2002. Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) on Days 1 and 8; this regimen was repeated every 5 weeks. Concurrent radiotherapy involved 60-Gy irradiation (30 fractions) for 8 weeks with a 2-week break. Responders received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1. Final analysis was conducted in March 2007. Survival and late toxicities were monitored for 5 years.
Results: The characteristics of the 76 patients enrolled were as follows: median age, 61 years; male/female, 68/8; performance status 0/1, 59/17 patients; Stage IIA/IIB/III, 26/12/38 patients. Of the 74 eligible patients, 46 (62.2%) achieved complete response. Median survival time was 29 months, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively. Acute toxicities included Grade 3/4 esophagitis (17%), nausea (17%), hyponatremia (16%), and infection without neutropenia (12%). Late toxicities comprised Grade 3/4 esophagitis (13%), pericardial (16%) and pleural (9%) effusion, and radiation pneumonitis (4%), causing 4 deaths.
Conclusions: CRT is effective for Stage II–III ESCC with manageable acute toxicities and can provide a nonsurgical treatment option. However, further improvement is required for reduction in late toxicity. © **2010 Elsevier Inc.**

Esophageal squamous cell carcinoma, Chemoradiotherapy, Long-term toxicity, Salvage surgery.

INTRODUCTION

Esophageal cancer, a highly virulent malignancy, was responsible for 11,182 deaths in Japan in 2005, accounting for 3.4% of the country's total cancer deaths (1), with 35–40% of the patients diagnosed with Stage II–III disease. When this study was planned, the standard treatment for Stage II–III esophageal squamous cell carcinoma (ESCC) in Japan was esophagectomy with three-field lymph node dissection, followed by postoperative chemotherapy; the 5-year survival rate is reported to be 36.8–61% (2–4), with a high morbidity rate.

Chemoradiotherapy (CRT) has proved effective against resectable/unresectable ESCC. The Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of CRT with cisplatin (CDDP), 5-fluorouracil (5-FU), and concurrent irradiation (50.4 Gy) over radiotherapy alone (64 Gy) in patients with T1–3N0–1M0 esophageal cancer (5), in which the final outcome showed a 5-year survival rate of 26% in the CRT arm compared with 0% in the

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radiation-alone arm (6). Therefore, CRT is recognized as the standard noninvasive treatment for patients with localized esophageal cancer who opt for nonsurgical treatment.

CRT was introduced in Japan in the early 1990s as a treatment for potentially unresectable locally advanced ESCC. In a Phase II trial, 18 of 54 (33%) patients with clinical T4 and/or M1 lymph node ESCC, who received CDDP/5-FU with concurrent 60-Gy irradiation, achieved complete response (CR) with a 3-year survival rate of 23% (7). Since then, CRT has been clinically indicated for patients with resectable ESCC who refuse surgical resection. In a retrospective analysis, 55 patients with T1–3NanyM0 ESCC, who received CRT with CDDP, 5-FU, and concurrent 60-Gy irradiation, showed a CR of 70% and a 5-year survival rate of 46%, suggesting comparable outcomes with surgery (8). However, the results were retrospective. Thus, we conducted a Phase II study to evaluate the efficacy and toxicity, particularly the long-term outcome, of CRT for Stage II–III ESCC.

PATIENTS AND METHODS

Eligibility

The eligibility criteria were as follows: pathologically confirmed thoracic ESCC; clinical Stage II–III excluding T4 (T1N1M0 or T2–3N1–0M0: International Union Against Cancer [UICC] 1997); Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0 or 1; and age, 20–70 years. Patients who had previously undergone therapy for esophageal cancer or chemotherapy/radiotherapy for other malignancies and who previously had had other active malignancies were excluded. All the patients had to meet the following laboratory criteria within 14 days before registration: leukocytes $\geq$3,000/mm^3; platelet count $\geq$100,000/mm^3; hemoglobin level $\geq$10 g/dL; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq$2 $\times$ the upper normal limit at the institution; total bilirubin $\leq$1.5 mg/dL; serum creatinine $\leq$1.2 mg/dL; creatinine clearance $\geq$50 mL/min; PaO_2 $\geq$70 mm Hg; and no major electrocardiogram abnormalities. Written informed consent was obtained from all the patients. The study protocol was approved by the JCOG Clinical Trial Review Committee and institutional review boards of the participating institutions.

Chemotherapy

Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) with adequate hydration and antiemetic coverage on Days 1 and 8; this regimen was repeated every 5 weeks. Responders additionally received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1 (Fig. 1), repeated every 4 weeks. No further treatment was administered to patients with CR until disease progression. Additional chemotherapy courses were optional for patients with visible disease.

Administration of both chemotherapy agents was discontinued until toxicity improved to $\leq$Grade 2. The doses were reduced by 25% in the subsequent course after at least one of the following toxicities was observed: leukocytes <1,000/mm^3; platelet count <30,000/mm^3; total bilirubin >2.0 mg/dL; serum creatinine $\geq$2.0 mg/dL; Grade 3/4 stomatitis; or Grade 3/4 esophagitis. Total parenteral nutrition was provided as necessary. Treatment was terminated when disease progression was observed, patients refused to continue, or recovery from toxicity delayed the initiation of the second course by >3 weeks from the planned schedule.

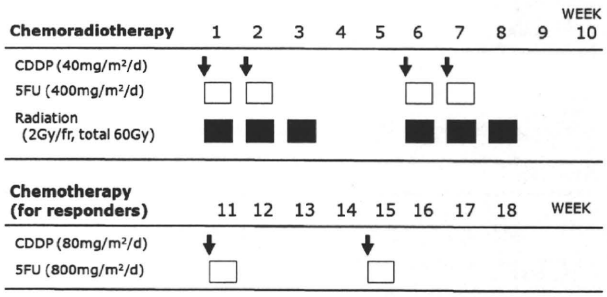

Fig. 1. Protocol scheme.

Radiotherapy

Radiotherapy was delivered using megavoltage ($\geq$6 MV) x-rays; a total dose of 60 Gy was administered in 30 fractions. A 2-week break was provided after 30-Gy irradiation, and radiotherapy was resumed on Day 36 with the second chemotherapy course. The clinical target volume (CTV) for 60-Gy irradiation included the primary tumor plus a 5-cm craniocaudal margin, and the metastatic lymph nodes plus a 1-cm margin. Planning target volume was defined as CTV plus 5- to 20-mm margins for uncertainty. Elective nodal irradiation (40 Gy) of mediastinal and perigastric lymph nodes for all cases, cervical lymph nodes for an upper thoracic primary tumor, and celiac lymph nodes for a lower thoracic primary tumor was also performed. Three-dimensional computed tomography (CT) or X-ray simulation was performed, allowing two-dimensional anterior–posterior opposed fields and bilateral oblique boost. Heterogeneity-uncorrected doses were used.

Assessments

Esophagoscopy and CT were carried out after each course to assess the response. Primary tumor response was evaluated by endoscopy using the modified criteria of the Japanese Society for Esophageal Diseases (9). Complete response of lymph node metastasis was defined as the disappearance of all visible lymph node metastases on the CT or size reduction to $\leq$1 cm for $\geq$3 months after the completion of treatment. Overall CR was declared by an attending physician when CR at both a primary tumor and a lymph node was obtained without the appearance of a new lesion. Complete response was confirmed by reassessment at $\geq$4 weeks after the first assessment. Complete response cases were centrally reviewed, and CR was confirmed by extramural review of the CT scan and images of endoscopy.

Acute toxicities were assessed weekly during CRT and every 2 weeks during additional chemotherapy for 90 days after the completion of CRT. Toxicities were evaluated based on the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity, which first occurred 90 days after CRT initiation, was assessed using the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Statistical methods

The primary endpoint was overall survival (OS), which was defined as the time from the date of registration to that of death resulting from any cause, and it was censored at the date of the last follow-up for survivors. Progression-free survival (PFS) was defined as the time from the date of registration to that of disease progression or death resulting from any cause, and it was censored at the date of the last visit for patients without progression. Based on the JCOG 9204 trial results (2), in which the 3-year survival rate was 61% for esophagectomy with adjuvant chemotherapy, we initially calculated the sample size expecting a 3-year survival rate of 60%, with a threshold of 45%. With the alpha and beta error levels set at 0.05 and 0.2, respectively, the required number of eligible patients was 68. We finally decided on a sample size of 76, including ineligible patients. The planned accrual and follow-up periods after registration was closed were 1 and 2 years, respectively. For early termination of this study, an interim analysis was planned once 50% of the patients were accrued. A CR point estimate of <60% at the interim analysis would result in early termination of the study.

The JCOG 9204 had enrolled patients based on the pathologic stage after surgery, whereas we enrolled patients based on the clinical stage diagnosed from CT scans. Therefore, this study might include patients with more advanced stages than those in the JCOG 9204. Thus, the protocol was amended to recalculate the sample size from the expected 50% 3-year survival rate and a threshold of 35% in December 2000. The required sample size was 67. The target sample size remained unchanged. The second amendment in February 2007 prolonged the follow-up period to 5 years after the last enrollment to evaluate late toxicity. These amendments were approved by the Data and Safety Monitoring Committee of JCOG.

Secondary endpoints included CR rate, PFS, and acute and late adverse events. Time-to-event distribution was estimated using the Kaplan-Meier method, and confidence intervals (CIs) were calculated using Greenwood's formula. All analyses were performed using SAS Version 9.1.3 software (SAS Institute, Cary, NC, USA) at the JCOG Data Center, with the final analysis conducted in March 2007.

RESULTS

Patient characteristics

Seventy-six patients, whose characteristics are summarized in Table 1, were accrued between April 2000 and March 2002. The median age was 61 years (range, 39–70). Fifty-nine (78%) and 17 (22%) patients showed ECOG PS of 0 and 1, respectively. Fifty-two patients had T3 disease, and 50 had N1 disease. The clinical stages (UICC-TNM) were IIA for 26 patients, IIB for 12 patients, and III for 38.

Table 1. Patient characteristics

Characteristic	Patients (n = 76)	(%)
Male	68	89.4
Female	8	10.6
Age (y)		
Range	39–70	
Median	61	
Performance status		
0	59	77.6
1	17	22.4
Tumor location		
Upper	3	3.9
Middle	44	57.9
Lower	29	38.2
T factor		
T1	8	10.5
T2	16	21.1
T3	52	68.4
N factor		
N0	26	34.2
N1	50	65.8
Stage		
IIA	26	34.2
IIB	12	15.8
III	38	50.0

Response

Two patients were excluded from the efficacy analysis because of inadequate liver function and T4 disease diagnosed after registration (Fig. 2). Of the 74 eligible patients, 46 achieved CR, resulting in a CR rate of 62.2% (95% CI, 50.1–73.2). The confirmed CR rate in 23 patients with T1–2 disease was 78.3% (95% CI, 56.3–92.5), and that in 51 patients with T3 disease was 54.9% (95% CI, 40.3–68.9).

Survival

There were 49 deaths in the final analysis, and all except 5 patients were followed up for >5 years. The median survival time was 2.4 years (Fig. 3); the 3- and 5-year survival rates were 44.7% (90% CI, 35.2–53.8) and 36.8% (95% CI, 26.1-47.5), respectively. The lower limit of 90% CI for the 3-year survival rate exceeded the threshold of 35%, and the

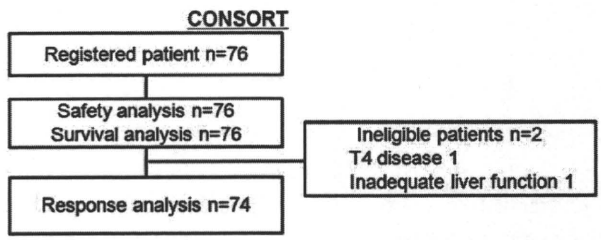

Fig. 2. Consolidated Standards of Reporting Trials diagram.

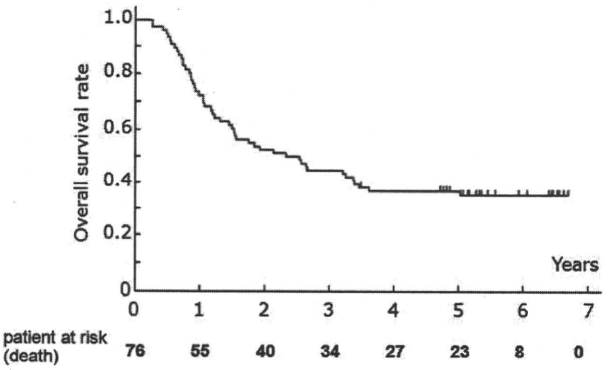

Fig. 3. Overall survival of the 76 patients enrolled in the study.

null hypothesis was rejected (p = 0.019). The median PFS was 1 year; the 3- and 5-year PFS rates were 32.9% and 25.6%, respectively (Fig. 4).

Acute toxicity

Data of adverse events for all 76 patients occurring within 90 days after CRT completion are shown in Table 2. Grade 4 leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 1.3%, 1.3%, 2.6%, and 0% of the patients, respectively, whereas Grade 3/4 esophagitis, nausea, infection without neutropenia, and hyponatremia were observed in 17%, 17%, 12%, and 16% of the patients, respectively.

Fifty-three (69.7%) patients completed the 2-course CRT and 2-course additional chemotherapy. Seventy-two (95%) patients received the full dose (60 Gy) of radiation. The treatment protocol was terminated in 23 patients because of disease progression (n = 10), toxicity (n = 11), patient refusal (n = 1), and other reasons (n = 1). One early death occurred from esophageal perforation caused by disease progression 21 days after CRT completion. A relationship between early death and the treatment protocol was considered unlikely by the Data and Safety Monitoring Committee.

Late toxicity

Late toxicity data are shown in Table 3. Grade 3–4 late toxicities included pleural (9%) and pericardial (16%) effusion, stenosis, or esophageal fistula (13%), and radiation pneumonitis (4%). Four (5.3%) patients possibly died of treatment-related late toxicity at 3.1, 8.5, 21.3, and 27.8 months after registration. The cause of death were pneumonitis (n = 2), pericarditis (n = 1), and pleural effusion (n = 1). There was no evidence of residual or recurrent disease in these patients. The proportion of any Grade 3/4 late toxicity was 30.1% after 5 years from the initiation of chemoradiation.

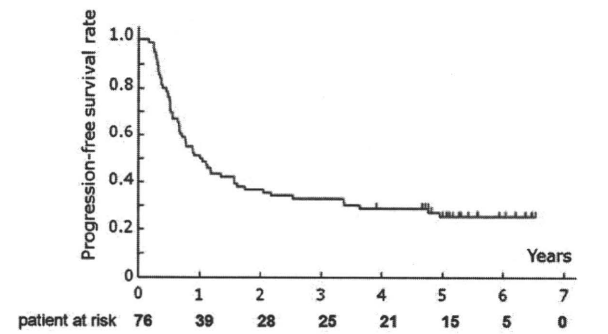

Fig. 4. Progression-free survival rate of the 76 patients enrolled in the study.

Salvage treatment

Twenty-six (34.2%) patients had residual disease or locoregional recurrence without distant metastasis after CRT. Because of inadequate conditions or patient refusal, 7 and 5 patients received chemotherapy and the best supportive care, respectively; the remaining 14 patients received unplanned curative-intent salvage therapy. Eleven patients underwent salvage esophagectomy for residual (n = 4) and recurrent (n = 7) disease, and the remaining 3 patients underwent endoscopic treatment such as endoscopic mucosal resection (EMR) or argon plasma coagulation. The characteristics of the patients who underwent salvage surgery are described in Table 4.

The median time to salvage surgery after CRT initiation was 13.9 months (range, 4.0–22.7). Six patients underwent esophagectomy with two- or three-field lymph node dissection, 3 patients underwent simple esophagectomy, and 1 underwent only lymphadenectomy; 1 patient could not undergo any resection because of extensive lymph nodes metastasis detected at thoracotomy. Reconstruction was performed using a gastric tube in 7 patients who had R0 resection. There was no operative mortality or hospital death. The median survival time and 3-year survival rate for these 10 patients who received salvage esophagectomy was 16.7 months and 40% (95%C.I: 12.3%–67.0%), respectively.

Of the 3 patients who underwent endoscopic treatment, 1 had mediastinal lymph node metastasis 3 months after argon plasma coagulation, 1 died of surgery-related complication of the pharynx detected 1 year after EMR, and 1 survived for >5 years with no evidence of disease.

DISCUSSION

From the results, CRT for Stage II–III ESCC showed a CR rate of 62.2% (95% CI, 50.1–73.2), a 3-year survival rate of 44.7% (90% CI, 35.2–53.8), and a 5-year survival rate of 36.8% (95% CI, 26.1–47.5). The 3-year survival rate, which is the primary endpoint of this study, met the decision criteria.

Clinically, it is very important to know whether definitive CRT can achieve survival comparable with surgery plus postoperative adjuvant chemotherapy. In this regard, there were several differences in the background between the present study and JCOG 9204 (2) described in Statistical Methods. The study conducted after JCOG 9204, which compared preoperative and postoperative adjuvant chemotherapy comprising the administration of 5-FU and CDDP to Stage II–III esophageal cancer patients (JCOG 9907) (10), could be a reference for this study, because the patients were registered before surgery based on the clinical stage. In the recently

Table 2. Toxicity (n = 76)

Toxicity	NCI-CTC Version 2.0				
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Leukocytes	5	34	32	1	43
Neutrophils	17	31	19	1	26
Hemoglobin	13	35	15	2	22
Platelets	15	13	4	0	5
Dysphagia, esophagitis	29	14	13	0	17
Nausea	25	20	13	–	17
Vomiting	16	6	0	0	0
Diarrhea	10	5	1	0	1.3
Stomatitis/pharyngitis	15	9	6	0	8
Radiation dermatitis	18	4	0	0	0
Febrile neutropenia	–	–	1	0	1.3
Infection without neutropenia	7	8	8	1	12
Hyponatremia	40	–	11	1	16
AST	35	4	3	0	3.9
ALT	43	7	2	1	3.9
Creatinine	15	13	1	0	1.3

Abbreviations: NCI-CTC Version 2.0 = National Cancer Institute Common Toxicity Criteria Version 2.0; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

published results of JCOG 9907, the preoperative chemotherapy arm was highly superior to the postoperative chemotherapy arm in terms of OS. The 5-year survival rate of the postoperative chemotherapy arm in JCOG 9907 did not differ significantly from that in the present study, that is, 38.4% and 36.8%, respectively (10). By contrast, the 5-year survival rate of the preoperative chemotherapy arm in JCOG 9907 was 60.1%, although further follow-up is needed to verify the data. CRT may produce comparable outcomes with surgery plus postoperative adjuvant chemotherapy; however, surgery after preoperative chemotherapy is considered to be superior to CRT. Nevertheless, CRT is one of the treatment options for patients with Stage II and III ESCC because of its apparent advantage of preserving the esophagus, which may provide better quality of life.

Chemoradiotherapy achieves prolonged survival with possibly more late toxicity. Late toxicity after thoracic radiotherapy has been reported in patients with esophageal cancer, lung cancer, and Hodgkin's lymphoma (11–13). Some reports have described that long-term toxicity after CRT results in serious, life-threatening complications. In a previous study, 2 of 78 patients with CR after CRT died of myocardial infarction, and 8 (10.2%) died of pericardial or pleural effusion (14) Late toxicity after CRT against ESCC has not yet been investigated in detail, and early reports of trial outcomes generally seem to underestimate the risk of late toxicity in long-term survivors (15). In the present study, the incidence of ≥Grade 3 late toxicity was similar to that reported in a previous study (14). Most of these events occurred several years after CRT. It is considered that reduction in radiation dose, careful observation, and control of late toxicity may improve post-CRT survival. RTOG 94-05 demonstrated that a higher irradiation dose (64.8 Gy) in CRT was not advantageous with regard to survival and local control, compared with the standard dose (50.4 Gy) (16). One of the reasons was the low tolerability of the high-dose arm because of toxicity. Whereas decreasing the irradiation dose in radiotherapy is essential for reducing late toxicity, the radiation volume is also

Table 3. Late toxicity (n = 76)

Late toxicity	RTOG/EORTC late radiation morbidity scoring scheme					
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	≥Grade 4 (%)
Pleural effusion (nonmalignant)	24	5	7	0	9	0
Esophagus-related (dysphagia, stenosis, fistula)	11	4	4	6	13	8
Pericardial effusion	6	5	9	3	16	4
Radiation pneumonitis	33	6	2	1	4	1.3
Skin-related	3	0	0	0	0	0
Spinal cord—related	3	0	0	0	0	0

Abbreviation: RTOG/EORTC: radiation therapy oncology group/european organization for research and treatment of cancer.
four (5.3%) patients possibly died of treatment-related late toxicity: pericarditis (n = 1), pleural effusion (n = 1), and pneumonitis (n = 2).

Table 4. Characteristics and outcomes in patients who underwent salvage surgery

Characteristic	Patients (n = 11)	Characteristic	Patients (n = 11)
Male	11	Residual/Recurrent	4 /7
Female	0		
Age (y)		Surgical curability	
Range	46–70	R0	7
Median	59	R1 + R2	4
Tumor location			
Upper	0	Operative mortality or hospital death	0
Middle	6		
Lower	5	Relapse after surgery	8
Clinical stage*		No relapse	3
IIA	5		
IIB	0		
III	6		

* Clinical stage at the time of registration.

important. In this study, late toxicity might have been caused by the extended volume of irradiation, which corresponds to the dissected area in extended surgery. In the near future, three-dimensional conformal radiotherapy, which was not mandatory in this study, or other methods based on advanced technology such as intensity-modulated radiotherapy and proton therapy, may have potential advantages over conventional two-dimensional radiotherapy in terms of reduced doses for the heart. A clinical trial with these latest radiotherapy techniques is required (17).

Salvage treatment—*e.g.*, salvage surgery (18–20) or salvage EMR (21)—has recently been reported to have therapeutic potential for patients with local failure of CRT. In our study, one-third of the patients did not achieve CR, and 50% of the remaining patients had recurrence after achieving CR. For the latter, salvage treatment should be indicated, if applicable. Mucosal disease can be removed by EMR, and locoregional residual or recurrent disease can be curatively resected by surgery. It has been reported that 6–34% of patients undergo salvage esophagectomy after definitive CRT (22, 23). Although a high rate of hospital deaths (6–33%) is observed compared with that after surgery without preoperative therapy, some patients achieve long-term survival with a 5-year survival rate of 25–35% (24–26). In the present study, 11 (14.5%) patients underwent salvage esophagectomy and 7 had R0 resection. There was no operative mortality or hospital death. The limitations of salvage surgery include patient tolerance, capability of medical staff, and early detection of residual or recurrent disease; however, salvage esophagectomy can achieve long-term survival. Some patients benefit from salvage surgery after definitive CRT; therefore, this procedure is worth further investigation.

Neoadjuvant CRT has recently been recognized as a standard therapy for resectable esophageal cancer in Western countries. According to CALGB 9781, CRT followed by surgery prolonged survival (median survival time, 4.48 vs. 1.79 years) compared with surgery alone in the treatment of esophageal cancer (27). However, most participants in CALGB 9781 had esophageal adenocarcinoma. Meta-analysis has revealed the survival benefit of neoadjuvant CRT in patients with esophageal adenocarcinoma (28). According to FFCD 9102, which included 90% patients with squamous cell carcinoma, surgery after neoadjuvant CRT (40 Gy) and continuation of CRT to 60 Gy without surgery had the same impact on survival and quality of life for responders as induction CRT (29). The results of a randomized trial from Germany, in which 172 ESCC patients randomly received CRT with or without additional surgery, indicated equal efficacy of surgery and CRT. The median survival times were 16.4 months and 14.9 months, respectively, and the 2-year survival rates were 39.9% and 35.4% with and without surgery, respectively (30). This suggests that CRT, which can preserve organ function, is equally effective as surgery for responders. For nonresponders, salvage surgery can be a therapeutic option. Importantly, which types of patients are benefited by salvage surgery or how the surgical procedure is performed after CRT should be prospectively evaluated. We are planning a Phase II trial of CRT for resectable ESCC, followed by salvage surgery for residual or recurrent disease.

CONCLUSION

Chemoradiotherapy is effective for Stage II–III ESCC with manageable acute toxicities and can provide a noninvasive treatment option. However, further improvement is required for reduction in late toxicity.

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A Simple Respiratory Indicator for Irradiation during Voluntary Breath Holding: A One-Touch Device without Electronic Materials[1]

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Purpose: To evaluate the use, structural principles, operation, and acquired reproducibility of a respiratory monitoring device to be used for voluntary patient breath holding.

Materials and Methods: Evaluation was performed of a respiratory monitoring device that enables determination of the respiratory level in a patient by measuring the movement of two contacts on the abdomen and chest wall. Neither metallic nor electronic materials are used in the mechanics for this device. The initial study group comprised 21 consecutive patients (15 men, six women; mean age, 75 years; range, 56–92 years) with lung or abdominal tumors who underwent examination with the device and computed tomography (CT) for three-dimensional reproducibility of lung base position during voluntary breath holding with or without use of the device.

Results: One patient with mild dementia was excluded; in most of the remaining 20 patients, high reproducibility of the breath-holding position was achieved in a short time with the device. In these 20 patients who were able to adapt to use of the device, three-dimensional mean maximum differences in lung base position during three random voluntary breath holds were 2.0 mm along the cranial-caudal axis, 1.5 mm along the anterior-posterior axis, and 1.2 mm along the right-left axis. The differences in all axes were significantly smaller with use of the respiratory monitoring device than without the device.

Conclusion: The device demonstrates satisfactory reproducibility of voluntary patient breath holding easily and inexpensively and may offer a convenient device for easy use during irradiation with voluntary breath-holding conditions that require a small internal margin.

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During radiation therapy to the abdominal and thoracic organs, minimizing the size of the radiation field while allowing for organ motion is important to reduce normal tissue toxicity and improve therapeutic effectiveness. Although image-guided radiation therapy systems are effective for reducing interfractional setup margins, intrafractional internal motion caused by patient respiration cannot be controlled. Interest in techniques designed to control respiratory movements has been growing since the mid-1990s, with the development of approaches including breath holding (1–3), respiratory gating (4,5), and beam tracking (6). Of all these techniques, we consider breath holding to be the most obvious and simplest solution to reduce uncertainties related to movements induced by breathing and to increase the reproducibility of treatment. Two approaches can be used for breath holding: active breathing control (1) and voluntary breath holding (2,3). Although these methods initially appear similar, the former is relatively invasive in nature for patients, since breathing is controlled forcibly by a valve in the spirometer. Voluntary breath holding thus appears preferable for patients with lung cancer in whom pulmonary function is apt to be poor. Though some teams have tried nonmonitored voluntary breath holding with a certain degree of success (7–10), these techniques have been considered uncertain, and various respiratory monitoring apparatuses have been introduced to improve the reproducibility of breath holding. However, as most existing apparatuses are complex, costly, or inaccurate (11), voluntary breath-holding techniques that use such devices are again unsuitable for small and intermediate-sized medical facilities with inexperienced staff.

We therefore aimed to develop a method of self–breath holding that can be performed as simply, nonelectronically, noninvasively, and inexpensively as possible. The purpose of our study was to evaluate the use, structural principles, operation, and acquired reproducibility of a newly developed simple respiratory monitoring device that has two contacts on the abdominal and chest wall of the patient.

Advances in Knowledge

- We developed a respiratory indicator that is simpler and less expensive than other conventional indicators.
- This device enables determination of the respiratory level in a patient by measuring movement of two contacts on the abdomen and chest wall without needing electronic materials.
- Our preliminary experiences show that this device is easily used during irradiation with voluntary breath-holding conditions that require a small internal margin.

Materials and Methods

All study protocols were approved by the institutional review board, and all patients provided written informed consent prior to participating in the study.

Technical aspects of the device including the structural principles, materials used, and the indicator rotation setting in relation to the contact movement were partially suggested by the coauthor (H.K.) who is an investigator at Apex Medical (Tokyo, Japan). The company provided no other material or financial support and had no control or other involvement in the study.

Implications for Patient Care

- The device uses a simple method to achieve good reproducibility for voluntary patient breath holding during irradiation.
- The device can minimize intrafractional respiratory organ motion nonelectronically, noninvasively, and inexpensively.
- The device may offer substantial benefits to facilities that lack highly trained staff and resources.

Structure and Operation of the Device

Figure 1 shows the main body of the device, which consists of thoracic and abdominal contacts, a stand, a mechanical unit, and a respiratory level indicator panel. The framework of the device is hollow and made of carbon. As a result, the effect of radiation absorption by the device on dose distribution of the irradiation field is negligible.

The device is normally used by placing the one contact each on the chest and abdomen of the patient, who lies in a supine position (Fig 2). The equipment used for the study in conjunction with the device included a whole-body computed tomography (CT) scanner (Hi-Speed DX/I; GE Yokogawa Medical Systems, Tokyo, Japan), and an x-ray simulator (SAT-20; Shimadzu, Kyoto, Japan).

Vertical motions of the chest and abdomen associated with breathing are detected by the thoracic and abdominal contacts, and movements of the contacts are added and converted to a rotational angle of a needle in the level meter. The contacts are designed such that a 1-cm movement on the body surface results in a rotation of 23° on the level meter. When both contacts move 1 cm in the same direction as a result of breathing by the patient, the indicator rotates by as much as 46°. The patient can thus control his or her breathing by watching the indicator.

The level indicator panel has two markers, red and yellow, that define the levels of full exhalation and full inhalation and one blue marker that defines

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See Materials and Methods for pertinent disclosures.

Figure 1

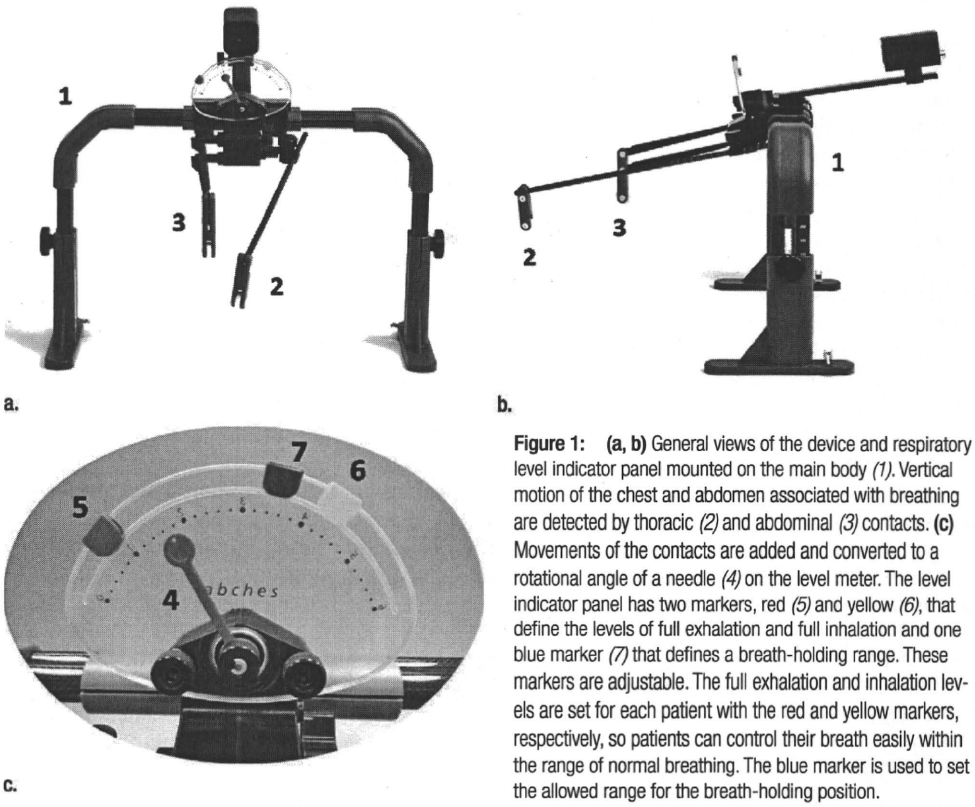


Figure 1: **(a, b)** General views of the device and respiratory level indicator panel mounted on the main body *(1)*. Vertical motion of the chest and abdomen associated with breathing are detected by thoracic *(2)* and abdominal *(3)* contacts. **(c)** Movements of the contacts are added and converted to a rotational angle of a needle *(4)* on the level meter. The level indicator panel has two markers, red *(5)* and yellow *(6)*, that define the levels of full exhalation and full inhalation and one blue marker *(7)* that defines a breath-holding range. These markers are adjustable. The full exhalation and inhalation levels are set for each patient with the red and yellow markers, respectively, so patients can control their breath easily within the range of normal breathing. The blue marker is used to set the allowed range for the breath-holding position.

a breath-holding range (Fig 1). The patient holds his or her breath to bring the indicator to the blue marker. In this way, CT scanning and irradiation can be performed accurately for the duration of patient-controlled breath holding.

The device has auxiliary components that include a mirror and a switch for the patient (Fig 2). The mirror allows the patient in the supine position to easily watch the level indicator. The switch is used by the patient to inform the radiotherapist of the breath-holding state, so that the radiotherapist can then perform treatment in collaboration with the patient.

The technician also can observe the device indicator needle remotely by means of a charge-coupled device monitor mounted on the patient table, and when the technician notices that the breath is not being held appropriately, the technician will assist the patient to improve control.

Setting of the Device and Instruction on Breath Holding

Initially, 21 patients who had been introduced consecutively to our department to undergo radiation therapy for lung or abdominal tumors were included as subjects, but one patient (92-year-old female) was excluded from the study because she was unable to understand the breath-hold technique owing to mild dementia. As a result, 20 patients were enrolled in the study. The background and clinical characteristics of the 20 patients are shown in Table 1. Nine patients had chronic pulmonary disease, and respiratory function parameters were below normal limits in seven of 20 patients.

The body of the patient was fixed with a vacuum pillow, and use of the device was explained to patients by showing them a fluoroscopic image of the diaphragm in respiratory motion. Using the device, subjects were taught to keep a regular respiratory rhythm within a uniform range on the indicator of the device. Signal waveforms of respiratory volume were acquired by using a spirometer (HI-801; Central Sports, Tokyo, Japan) during free respiration with and without use of the device. Subjects were then instructed to hold their breath during inspiration so as to maintain an identical position through voluntary breath holding.

Measurement of Reproducibility of Lung Base Position during Repeated Breath Holds

After patients fully understood and mastered voluntary breath holding with and without the use of the device, a set of three CT scans was obtained with the device and another set was obtained without the device (ie, six CT scans total), to obtain randomly timed images of 2 mm thickness in the vicinity of the lung base. The CT scanning interval

Figure 2

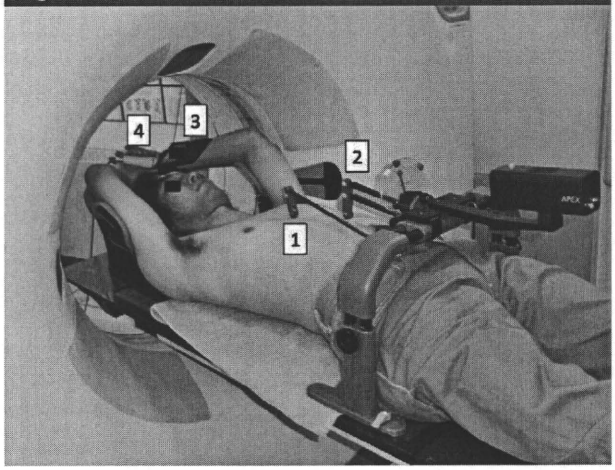


Figure 2: View of the main body of the device in use on a patient. Two contacts are placed on the chest *(1)* and abdomen *(2)* of a patient lying in a supine position. Auxiliary components on the device include a mirror *(3)* and a switch *(4)* for the patient. The height of the device is adjusted to the body size of each patient to ensure that the two contacts touch the abdomen and thorax.

Table 1

Patient Characteristics

Characteristic	Finding
Total no. of patients	20
Men	15
Women	5
Age (y)	56–86 (74)
Men	56–84 (72)
Women	72–86 (77)
Smoking index*†	
0–200	6
200–600	10
>600	4
Tumor site†	
Thoracic	16
Abdominal	4
ECOG performance status	0–2 (1)
$FEV_{1.0}$ (mL)	650–2350 (1520)
SaO_2 (mmHg)	65–90 (76)

Note.—Unless otherwise indicated, data are ranges, and numbers in parentheses are medians. ECOG = Eastern Cooperative Oncology Group, $FEV_{1.0}$ = forced expiratory volume in the first second, SaO_2 = arterial oxygen saturation.

*Average daily number of cigarettes multiplied by years.

† Data are numbers of patients.

was approximately 5 minutes. The first three scans were obtained during breath holding by using the device; the next three scans were obtained without the device. On the 2-mm-thick images in the vicinity of the lung base, an arbitrary point for measuring reproducibility of repeated breath holds was set on a clear peripheral vascular structure, and the maximum difference in measurement point for the three CT scans was calculated along three axes: cranial-caudal, anterior-posterior, and right-left. The detailed method for measuring reproducibility has been described previously (7).

Statistical Analysis

The statistical significance of disparities in maximum differences of lung base position in all patients with and without the device was determined by using a paired *t* test. All probabilities were two-tailed, with $P < .05$ considered to indicate a statistically significant difference. Statistical calculations were performed by using statistical software (StatView, version 5; SAS Institute, Cary, NC).

Results

Effect of the Device on Breathing

Figure 3 shows examples of respiratory volume curves measured with the spirometer obtained during free breathing without the device and under an instruction to breathe within a uniform range using the device. The respiratory volume curve obtained by using the device was more regular than that without the device.

Reproducibility of Breath Holding

All 20 patients practiced self-controlled breath holding by using the respiratory monitoring device. The mean time necessary for each of the 20 patients to be instructed on the use of the device and to master voluntary breath holding with and without the device was 20 minutes (range, 15–30 minutes). Mean duration of each breath hold was 18 seconds (range, 10–40 seconds).

Among the 20 patients who understood the breath-holding method, reproducibility of the measurement point during breath holds obtained by using the device was compared with that obtained without the device. The results are shown in Table 2. For the 20 patients, mean maximum differences in the measurement points obtained with and without the device, respectively, were 2.0 and 4.2 mm along the cranial-caudal axis, 1.5 and 2.8 mm along the anterior-posterior axis, and 1.2 and 2.0 mm along the right-left axis. Differences in all axes were significantly smaller ($P < .05$) with the device than without the device.

Case

An electronic portal imaging device was used to evaluate the reproducibility of tumor position during each radiation therapy session. Real-time electronic portal imaging was performed five to 10 times during each fraction. Examples of CT images and intrafractional electronic portal images in the vicinity of the tumor during voluntary breath holding with the device obtained before and during radiation therapy are shown in Figure 4 and 5, respectively.

Discussion

A widely used voluntary breath-holding technique is performed with a spirometer connected to a screen or video glasses

Figure 3

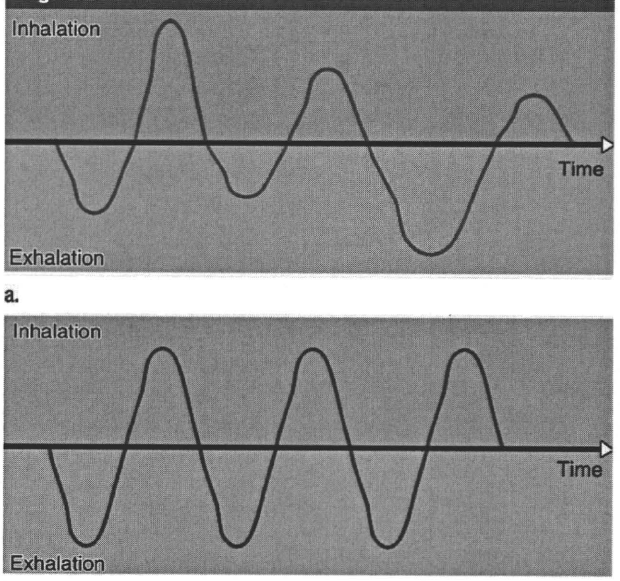


Figure 3: Examples of respiratory volume curves measured by using spirometry (HI-801; Central Sports, Tokyo, Japan) obtained during **(a)** free-breathing and **(b)** an instruction to breathe within a uniform range with the device.

Table 2

Reproducibility of Breath-holding Position of the Lung Base with and without the Device

Axis	With Device (mm)	Without Device (mm)
Craniocaudal direction		
Mean ± standard deviation*	2.0 ± 1.3	4.2 ± 2.2
Range	0–4	0–10
Anteroposterior direction		
Mean ± standard deviation*	1.5 ± 1.2	2.8 ± 1.8
Range	0–3.6	0.3–4.0
Left-right direction		
Mean ± standard deviation*	1.2 ± 1.1	2.0 ± 1.5
Range	0.0–3.0	0.3–3.8

* Differences in all axes were significantly smaller ($P < .05$) with this system than without it.

and indicates in real time, for the technicians and/or patient, the desired and actually achieved levels of breath hold (2,3). Hanley et al (2) used a voluntary deep-inspiration breath-hold system with a spirometer for patients with non–small cell lung cancer, and reported an intra–breath-hold reproducibility of 1.0 mm ± 0.9 and an inter–breath-hold reproducibility of 2.5 mm ± 1.6. In regard to intrafraction reproducibility of breath-holding positions, our technique using the device was not inferior to these other breath-hold techniques and devices.

The method performed with the present device has some merits for voluntary breath-holding technique. The greatest merit of the device is the simplicity of the mechanism and structure and convenience for patients and radiation therapy staff. To our knowledge, no other devices have been described that do not use electronic materials. Setting of other existing systems is regarded to be relatively more complicated than that of the present device. This device is also easy to install and is inexpensive. While most small and intermediate-sized medical facilities do not have equipment to compensate for respiratory motion, because such facilities have insufficient time, manpower, and/or money to introduce complicated irradiation schemes, our device appears highly effective for solving the above-mentioned problems.

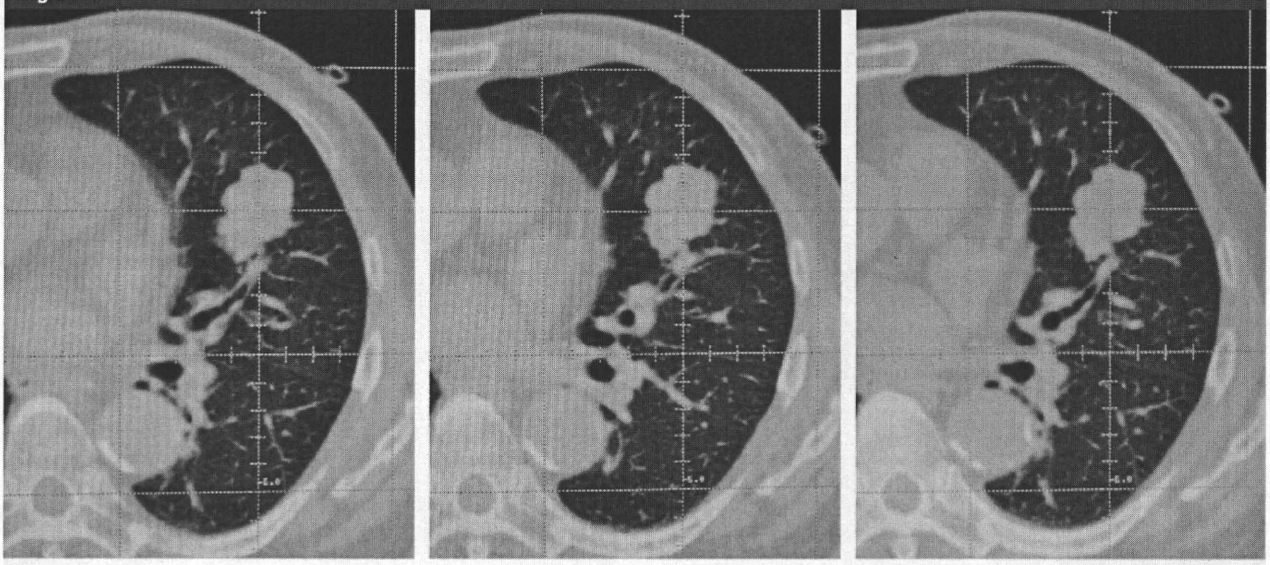
In addition, existing commercially available respiratory monitoring systems, such as the Real-time Position Management system (Varian, San Francisco, Calif) and the Anzai motion-monitoring system (AZ-773V; Anzai Medical, Tokyo, Japan), have only one detection point for respiratory monitoring and may not be able to capture precise breathing phases, which are affected in a complex fashion by the respiratory motions of the thorax and abdomen. While Mageras et al (12) and Vedam et al (13) reported a good phase relationship between abdominal and diaphragm motions, Nakamura et al (14) and Ahn et al (15) reported some differences between lung tumor and abdominal motions. A hysteresis curve was also observed. In contrast, with the present device, two detection points can be set arbitrarily on the chest and abdomen. This may allow synthesis of the movements measured at two sites, and we have been investigating whether the device can achieve more precise monitoring than other devices using one detection point.

Moreover, the device is versatile and enables a therapeutic procedure that normally requires high precision. The range of stabilized respiration was better with our device than without it (Fig 3). The device is also helpful for regulating breathing levels in a steady range and thus may be useful for gated or tracking radiation therapy.

Finally, the device has the great merit of requiring active patient involvement in switching and voluntary breath holding. When using the device, it is most important that the patient understands the purpose and nature of the method. A report of Task Group 76 of the American Association of Physics in Medicine (16) stressed that breath control requires active participation of the patient. This device contributes to such participation in treatment.

Carlson et al (17) reported good breath-hold reproducibility by using a bellows-based breath-hold monitoring

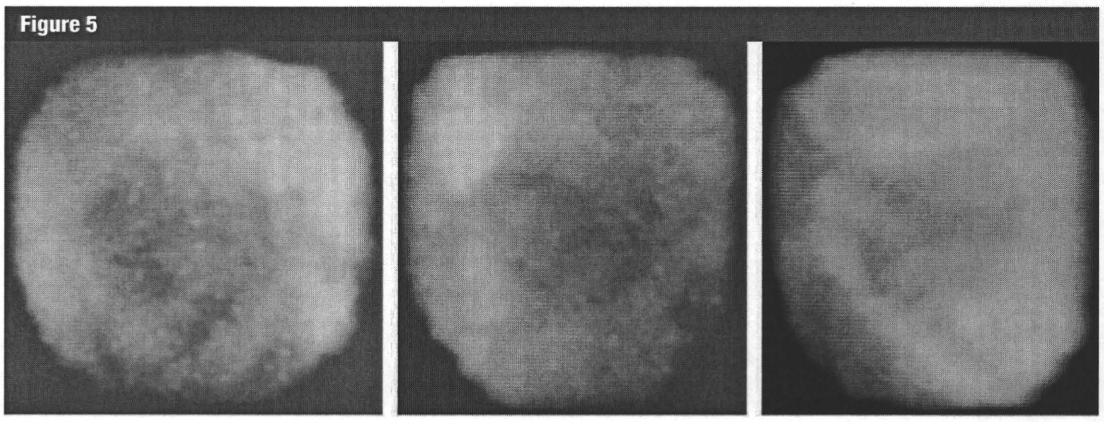
Figure 4



a. b. c.

Figure 4: CT images obtained during voluntary breath holding with the device. Before every session of radiation therapy, a set of three CT scans is performed to obtain randomly timed images of 2 mm thickness in the vicinity of the tumor. **(a–c)** Images obtained with the first, second, and third scan, respectively. The scanning interval was approximately 5 minutes. Maximum differences in tumor position in craniocaudal, anteroposterior, and right-left directions on three CT studies were 1, 0.7, and 0.5 mm, respectively.

Figure 5



a. b. c.

Figure 5: Example of intrafractional electronic portal images obtained during radiation therapy during voluntary breath holding with the device. Radiation therapy was performed with 10 noncoplanar static ports. **(a–c)** Three of the 10 portal images show that the tumor shadow lay appropriately on the planned position in each port.

and feedback system for CT-guided biopsy of the lung and upper abdomen. The basic components of the system are a Velcro belt with expandable bellows, a light-emitting diode monitor for patient feedback, and a system control unit. Variation in the length of the bellows causes a pressure change within the tubing, which is measured with a pressure-sensitive transducer. Although no detailed reproducibility of breath hold using this system was described in the report, the patient feedback system resembles our own. The device used in our study may also contribute to such operations of interventional radiology requiring good breath-hold reproducibility.

Applicability of the device must be established for each patient during preliminary practice sessions. Moreover, some key points should be noticed when patients are instructed on how to hold their breath. We routinely instruct patients to maintain smooth and regular breathing before breath holding. It is also important to educate patients

not to use abdominal muscles to adjust the indicator. If a patient deviates from these instructions, a large error can be produced that exceeds the estimated error. Sufficient instruction and practice are essential to achieving good reproducibility with the device.

In summary, we developed a simple and accurate respiratory monitoring indicator for irradiation during self-controlled voluntary breath holding that will offer substantial benefits to all facilities even if they lack highly trained staff and resources.

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