Clinical Study
Four-Dimensional Computed Tomography Based Respiratory-Gated Radiotherapy with Respiratory Guidance System: Analysis of Respiratory Signals and Dosimetric Comparison

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Purpose. To investigate the effectiveness of respiratory guidance system in 4-dimensional computed tomography (4DCT) based respiratory-gated radiation therapy (RGRT) by comparing respiratory signals and dosimetric analysis of treatment plans. Methods. The respiratory amplitude and period of the free, the audio device-guided, and the complex system-guided breathing were evaluated in eleven patients with lung or liver cancers. The dosimetric parameters were assessed by comparing free breathing CT plan and 4DCT-based 30–70% maximal intensity projection (MIP) plan. Results. The use of complex system-guided breathing showed significantly less variation in respiratory amplitude and period compared to the free or audio-guided breathing regarding the root mean square errors (RMSE) of full inspiration \((P = 0.031)\), full expiration \((P = 0.007)\), and period \((P = 0.007)\). The dosimetric parameters including \(V_{5\text{ Gy}}\), \(V_{10\text{ Gy}}\), \(V_{20\text{ Gy}}\), \(V_{30\text{ Gy}}\), \(V_{40\text{ Gy}}\), and \(V_{50\text{ Gy}}\) of normal liver or lung in 4DCT MIP plan were superior over free breathing CT plan. Conclusions. The reproducibility and regularity of respiratory amplitude and period were significantly improved with the complex system-guided breathing compared to the free or the audio-guided breathing. In addition, the treatment plan based on the 4D CT-based MIP images acquired with the complex system guided breathing showed better normal tissue sparing than that on the free breathing CT.

1. Introduction

Radiation therapy (RT) has evolved with the state-of-the-art technology with the purpose of giving higher doses to the tumors and lower doses to the surrounding normal tissues to maximize tumor control and minimize toxicities. The four-dimensional RT (4DRT), adding the fourth element “time” to the three-dimensional conformal RT (3DCRT), has been introduced and actively performed in daily practice in the same vein. Organs in the thorax and the abdomen are mostly affected by the respiratory motion moving up to 10–40 mm according to the literature [1, 2]. Respiration is quasiperiodic with a relatively predictable pattern in contrast to the arbitrary changes including peristalsis, expansion, contraction, and incidental cough which are difficult to predict [3]. The respiration-gated RT (RGRT) using the 4DRT technique permits selectively treating specific respiratory phases in the light of target location according to the organ movement and increasing therapeutic efficiency [4, 5]. Larger fields with larger safety margins to the target volumes were generally used to overcome the uncertainties during the treatment in the past [6]. However, targets have been getting smaller and more conformal with precise tumor localization for increasing tumor control and reducing the risk of toxicities. There have been several techniques to reduce the margins caused by the respiratory motion. These are breath holding techniques including active breathing control (ABC), abdomen compression, deep inspiration breathing hold technique (DIBH), respiratory gating technique, real-time tumor-tracking RT (RTRT), multileaf collimator...
(MLC) sequencing technique, couch tracking technique, and cyberknife robot RT [7–14]. Of these, gating technique
denotes “beam-on” during the specific respiration phases and
“beam-off” during the other phases as shown in Figure 1.
To ensure the regularity and reproducibility of respiration
during the RGRT, the audio-guided or the video-guided
feedback techniques have been suggested and shown to be
beneficial when compared to the free breathing [15, 16]. The
aim of this study was to investigate the effectiveness of respi-
ratory guidance system including audio and visual devices in
4-dimensional computed tomography (4DCT) based RGRT
by comparing respiratory signals of free breathing (no feed-
back), audio-guided breathing, and complex system-guided
breathing including audio and visual feedback.

2. Materials and Methods

2.1. Patients. Eleven patients were enrolled in an Institutional
Review Board-approved respiratory guidance system proto-
col for 4D RGRT from March 2011 to July 2013 in Korea
University Guro Hospital. The inclusion criteria were that
the patient (1) was diagnosed as a tissue-confirmed liver
or lung cancer; (2) was over 18 years of age; (3) was not
oxygen-dependent; (4) has Eastern Cooperative Oncology
Group Performance Status (ECOG PS) of 0–2; (5) showed the
diaphragmatic or visible tumor movement of more than 1 cm
in a craniocaudal direction in a X-ray fluoroscopy; (6) had
given signed informed consent.

2.2. The Respiratory Guidance System. The respiratory guid-
ance system reflecting the real-time breathing status for the
4DCT and the RGRT consisted of two parts: the audio-
component and the visual component. The audio-component
was composed of the motion picture expert group 1 audio
layer 3 (MP3) and earphones installed with voice files guiding
the patient’s respiration from 10 to 22 times per minute which
were recorded according to the individual speed of breathing
(Figure 2). For the visual components, the patients were able
to choose one of the three types of visual devices showing
the patient’s real time breathing signals: 17-inch liquid crystal
display (LCD) monitor (Multisync LCD 1770NX, NEC), 8-
inch light emitting diode (LED) monitor (CT-M080B LED,
WINDOM), or goggles (VUZIX, iWear VR920, USA). The
monitor types were installed to the couch by monitor arm
with six joints and were preferred for the patients wearing
glasses (Figure 3).

2.3. Acquisition of Respiratory Signals. The individual
patient’s respiration was assessed by a separate session for
respiration training to determine the best fitted speed of
breathing of the audio instruction. The free breathing (no
feedback), the audio-guided breathing, and the complex
system-guided breathing including audio and visual feedback
were applied to the patients and the respective respiration
signals were collected for 5 minutes during the separate
respiration training session and during the simulation
(Figure 4). We used the Real Time Position Management
(RPM) system (Varian Medical Systems, Palo Alto, CA) to
acquire the patients’ respiratory traces during the training
session and the 4DCT simulation. The RPM system is
composed of infrared-reflecting marker box which is placed
on the patient’s chest wall near xyphoid process and a charge
coupled device (CCD) camera tracking the vertical motion
of the marker at a frequency of 30 frames per second. The
data collection and visualization are managed by a dedicated
software tool installed in the system. The signals of the free
breathing were acquired without any feedback. Then, the
signals of the audio-guided breathing were obtained with
breathe-in/breathe-out instructions. Finally the traces from
the complex system-guided breathing were collected with
the audio instruction as well as the real time visual feedback
displayed in the selected monitor or goggles (Figure 5).

2.4. Analysis of the Respiratory Signals. To evaluate the repro-
ducibility and regularity of the respiration, data of the first
and the last 15 seconds were excluded from the analysis
regarding the adaptation period for the beginning period
and time-related fatigue of the endmost period. The extreme
outlier was also ruled out to increase the reliability of the
results. The average of the three consecutive stable respiratory
cycles was set up as a reference and normalized to “0” for the
purpose of correlating signals from the different sessions and

![Figure 1: An example of the respiratory gating radiation therapy
during the specific period of respiration.]

![Figure 2: The audio device of the respiratory guidance system.](a) Bodies of the MP3 (white, pink) (b) Earphones]
patients. The average of the maximal inspiration (maxima), the maximal expiration (minima), and the period of the reference respiratory cycles were set as a standard, and the respective root mean square errors (RMSE) were calculated for the entire signals (Figure 6).

2.5. Acquisition of Simulation CT and Analysis and Comparison of Treatment Plans. Two sets of simulation CT were performed in each patient using BrightSpeed Elite CT (GE healthcare Technologies, Waukesha, WI): first acquisition of precontrast enhanced CT under free breathing condition and then second acquisition of intravenous contrast agent enhanced 4DCT with complex system-guided breathing. The slice thickness was 5mm. For the purpose of data reconstruction of 4DCT, the acquired images were sorted by 10 respiratory phases determined from the RPM system.
Figure 4: Examples of the free breathing, the audio-guided breathing, and the complex system-guided breathing (the arrow indicates a deviation caused by a transient positional change).

Figure 5: Patient setup with the complex system-guided respiration.

The gating ranges were set between 30% and 70% phases, and images of 30%, 40%, 50%, 60%, and 70% phases were reconstructed with maximum intensity projection (MIP) method. The datasets were imported to Eclipse planning system (Version 8.3, Varian, CA, USA) for contouring target volumes and organs at risk (OARs). The gross tumor volumes (GTVs) in both free breathing CT images and 4DCT based MIP images were delineated in each patient by the same radiation oncologist with appropriate window setting for lung and liver cancers, respectively. The clinical target volumes (CTVs) were created by adding 5 mm margin to the GTVs and additional 5 mm margins to the CTVs were allowed for the PTVs. To assess the dosimetric impacts on normal lung and liver, identical beam arrangements were generated in both free breathing CT images and 4DCT based MIP images. All of the plans used 3-4 coplanar beams and were normalized such that at least 95% of the PTV received the prescription dose. The treatment plans based on the free
breathing CT were generated with the PTVs plus 1.5 cm margins and those on the 4DCT based MIP images were with the PTVs plus 1.0 cm since the internal margin of 5 mm was already reflected in the 4D simulation process. The dose fractionation schedules were 50 Gy in 5 fractions for the patients with lung cancer and 54 Gy in 18 fractions for those with liver cancer. The conformity index (CI), homogeneity index (HI), and prescription isodose target volume were calculated for the comparison of target coverage [17–19]. For the DVH comparison of normal lung and liver, $V_{5\text{ Gy}}$ (volume receiving 5 Gy), $V_{10\text{ Gy}}$ (volume receiving 10 Gy), $V_{20\text{ Gy}}$ (volume receiving 20 Gy), $V_{30\text{ Gy}}$ (volume receiving 30 Gy), $V_{40\text{ Gy}}$ (volume receiving 40 Gy), and $V_{50\text{ Gy}}$ (volume receiving 50 Gy) were used. The actual treatment was done with gating 4DRT ranging between 30% and 70% using Trilogy (Varian Medical Systems Palo Alto, CA). The Kolmogorov-Smirnov test was done for the continuous variables. The paired Student's $t$-test and one way ANOVA in SPSS version 20 (SPSS Inc., Chicago, IL) were used for the statistical analysis. The $P$ value of 0.05 or less was considered as statistically significant.

### 3. Results

The patients' characteristics were listed in Table 1. Among the enrolled eleven patients, 6 patients had hepatocellular carcinoma and 5 had non-small-cell lung cancer. The median age was 64 years (range 52–80 years). No patient had a surgery of liver or lung except 2 with liver cancer who underwent partial hepatectomy. The concurrent chemotherapy was not done in all patients. The average respiration per minute was 14.6 times ± 2.8 and the average cranio-caudal movement of diaphragm or tumor was 1.91 cm ± 0.70 in a routine fluoroscopy. The RMSEs of the maxima, the minima, and the period according to the three respiratory conditions were summarized in Table 2. Figure 7 presented the RMSE of the maxima and minima of individual patient. The RMSE of the maxima indicating full inspiration was 0.154 cm ± 0.096 for the free breathing, 0.119 cm ± 0.057 for the audio-guided breathing, and 0.061 cm ± 0.024 for the complex system-guided breathing ($P < 0.05$). When comparing the RMSE of the maxima between two groups, there was no significant difference observed between the free and the audio-guided breathing ($P = 0.216$). However, statistical significance was presented between the free and the complex system-guided breathing ($P = 0.004$) and between the audio-guided and the complex system-guided breathing ($P = 0.001$). The RMSE of the minima indicating full expiration was 0.220 cm ± 0.085 for the free breathing, 0.174 cm ± 0.095 for the audio-guided breathing, and 0.099 cm ± 0.053 for the complex system-guided breathing ($P < 0.05$). Two group comparisons in the RMSE of the minima showed significant differences for all combinations: the free versus the audio-guided breathing, $P = 0.020$; the free versus the complex system-guided breathing, $P = 0.000$; the audio-guided versus the complex system-guided breathing, $P = 0.020$, respectively. Meanwhile, the RMSE of the period was 0.951 sec ± 0.215 for the complex system-guided breathing, and 0.464 sec ± 0.215 for the complex system-guided breathing ($P = 0.009$) and between the audio-guided and the complex system-guided breathing ($P = 0.040$) were significant.

With the positive results, the 4DRT with complex system-guided breathing was applied to the actual treatment, and comparison between free breathing and 4DRT with complex system-guided breathing was performed in terms of dosimetric parameters. The CI, HI, and PITV were evaluated for the comparison of target coverage between plans of free breathing CT and 4D MIP CT. The CI of free breathing CT was $0.578 ± 0.525$ and that of 4D MIP CT was $0.637 ± 0.967$, respectively ($P = 0.096$). The HI was $1.043 ± 0.024$ and $1.033 ± 0.018$ for free breathing CT and 4D MIP CT, respectively ($P = 0.151$). Likewise, the PITV of free breathing CT was $0.997 ± 0.007$ and that of 4D MIP CT was $0.998 ± 0.007$, respectively ($P = 0.335$). There were no significant differences observed between the plans in terms of target coverage.

The DVH analysis was done for liver and lung for each applicable site (Table 3 and Figure 8). Normal liver volume receiving the same dose of radiation was less in plan on 4D MIP CT than on free breathing CT in patients with liver cancer: 78.75 ± 3.51 cc in free breathing CT versus 68.06 ± 6.68 cc in 4D MIP CT ($P = 0.024$) for $V_{5\text{ Gy}}$, 65.16 ± 7.83 cc versus 54.24 ± 10.45 cc ($P = 0.030$) for $V_{10\text{ Gy}}$, 43.84 ± 12.80 cc versus 35.22 ± 14.11 cc ($P = 0.048$) for $V_{20\text{ Gy}}$, 32.81 ± 12.68 cc versus 27.34 ± 14.68 cc ($P = 0.117$) for $V_{30\text{ Gy}}$, 25.79 ± 11.47 cc versus 21.53 ± 13.61 cc ($P = 0.069$) for $V_{40\text{ Gy}}$, and 19.39 ± 9.71 cc versus 16.06 ± 11.21 cc ($P = 0.067$) for $V_{50\text{ Gy}}$, respectively, as shown in Table 3(a). $V_{5\text{ Gy}}$, $V_{10\text{ Gy}}$, and $V_{20\text{ Gy}}$ showed statistically significant differences. Ipsilateral lung volume receiving same dose of radiation for patients with lung cancer showed similar results (Table 3(b)). There were significant differences observed in $V_{10\text{ Gy}}$, $V_{20\text{ Gy}}$, $V_{30\text{ Gy}}$, and $V_{40\text{ Gy}}$ and $V_{5\text{ Gy}}$, showed marginal significance: 48.97 ± 15.37 cc in free breathing CT versus 40.74 ± 11.07 cc in 4D MIP CT ($P = 0.051$) for $V_{5\text{ Gy}}$, 37.71 ± 17.89 cc versus 29.31 ± 15.22 cc ($P = 0.035$) for $V_{10\text{ Gy}}$, 23.02 ± 11 cc versus 16.03 ± 8.75 cc ($P = 0.018$) for $V_{20\text{ Gy}}$, 15.19 ± 9.24 cc versus 8.94 ± 5.46 cc.
### Table 1: The patients’ characteristics.

| Number | Age/sex | Diagnosis | Pathology | ECOG | Surgery | Concurrent chemotherapy | Breathing rate (/min) | Movement in fluoroscopy (cm) |
|--------|---------|-----------|-----------|------|---------|------------------------|------------------------|------------------------------|
| 1      | 65/F    | HCC⁷      | HCC⁷      | 1    | Yes     | No                     | 12                     | 2.5                          |
| 2      | 64/M    | HCC⁴      | HCC⁴      | 1    | Yes     | No                     | 15                     | 3                            |
| 3      | 56/F    | HCC⁴      | HCC⁴      | 1    | No      | No                     | 18                     | 1.8                          |
| 4      | 65/M    | HCC⁷      | HCC⁷      | 0    | No      | No                     | 17                     | 1.5                          |
| 5      | 62/M    | HCC⁴      | HCC⁴      | 0    | No      | No                     | 16                     | 1.2                          |
| 6      | 52/M    | HCC⁴      | HCC⁴      | 0    | No      | No                     | 10                     | 1.8                          |
| 7      | 59/M    | NSCLC⁶    | SCC⁵      | 1    | No      | No                     | 14                     | 2.0                          |
| 8      | 73/M    | NSCLC⁶    | SCC⁵      | 2    | No      | No                     | 12                     | 1.2                          |
| 9      | 80/M    | NSCLC⁶    | SCC⁵      | 1    | No      | No                     | 15                     | 1.3                          |
| 10     | 65/F    | NSCLC⁶    | AD⁥       | 0    | No      | No                     | 13                     | 1.5                          |
| 11     | 62/M    | NSCLC⁶    | AD⁥       | 0    | No      | No                     | 19                     | 3.2                          |

*Hepatocellular carcinoma.
†None-small-cell lung cancer.
‡Squamous cell carcinoma.
§Adenocarcinoma.

**Figure 7:** Root mean square error (RMSE) of the maxima and minima in all patients.
Figure 8: Comparison of dose volume histogram (DVH) of (a) liver and (b) lung between plans with free breathing CT (blue box and blue arrow) and 4D MIP CT (red box and red arrow) was shown.

Table 2: The root mean square error (RMSE) of maxima, minima, and period in the three breathing conditions.

(a) The RMSE of maxima (full inspiration)

|                | Free       | Audio-guided | Complex system-guided | P value |
|----------------|------------|--------------|-----------------------|---------|
| Maxima (cm)    | 0.154 ± 0.096 | 0.119 ± 0.057 | 0.061 ± 0.024         | 0.031   |

Free breathing versus audio-guided breathing (P = 0.216).
Free breathing versus complex system-guided breathing (P = 0.004).
Audio-guided breathing versus complex system-guided breathing (P = 0.001).

(b) The RMSE of minima (full expiration)

|                | Free       | Audio-guided | Complex system-guided | P value |
|----------------|------------|--------------|-----------------------|---------|
| Minima (cm)    | 0.220 ± 0.085 | 0.174 ± 0.095 | 0.099 ± 0.053         | 0.007   |

Free breathing versus audio-guided breathing (P = 0.020).
Free breathing versus complex system-guided breathing (P = 0.000).
Audio-guided breathing versus complex system-guided breathing (P = 0.020).

(c) The RMSE of period

|                | Free       | Audio-guided | Complex system-guided | P value |
|----------------|------------|--------------|-----------------------|---------|
| Period (sec)   | 0.951 ± 0.130 | 0.741 ± 0.213 | 0.464 ± 0.215         | 0.046   |

Free breathing versus audio-guided breathing (P = 0.370).
Free breathing versus complex system-guided breathing (P = 0.009).
Audio-guided breathing versus complex system-guided breathing (P = 0.040).
**Table 3:** Comparison of dose volume histogram (DVH) between plans with free breathing CT and 4D MIP CT.

(a) Liver

|                | Free breathing CT plan (cc) | MIP based plan (cc) | P value |
|----------------|-----------------------------|---------------------|---------|
| $V_{5 \text{ Gy}}$ | 78.75 ± 3.51                | 68.06 ± 6.68        | 0.024   |
| $V_{10 \text{ Gy}}$ | 65.16 ± 7.83               | 54.24 ± 10.45       | 0.030   |
| $V_{20 \text{ Gy}}$ | 43.84 ± 12.80              | 35.22 ± 14.11       | 0.048   |
| $V_{30 \text{ Gy}}$ | 32.81 ± 12.68              | 27.34 ± 14.68       | 0.117   |
| $V_{40 \text{ Gy}}$ | 25.79 ± 11.47              | 21.53 ± 13.61       | 0.069   |
| $V_{50 \text{ Gy}}$ | 19.39 ± 9.71               | 16.06 ± 11.21       | 0.067   |

(b) Ipsilateral lung

|                | Free breathing CT plan | MIP based plan | P value |
|----------------|------------------------|----------------|---------|
| $V_{5 \text{ Gy}}$ | 48.97 ± 15.37          | 40.74 ± 11.07 | 0.051   |
| $V_{10 \text{ Gy}}$ | 37.71 ± 17.89          | 29.31 ± 15.22 | 0.035   |
| $V_{20 \text{ Gy}}$ | 23.02 ± 11.20          | 16.03 ± 8.75  | 0.018   |
| $V_{30 \text{ Gy}}$ | 15.19 ± 9.24           | 8.94 ± 5.46   | 0.034   |
| $V_{40 \text{ Gy}}$ | 9.18 ± 3.88            | 4.90 ± 3.18   | 0.035   |
| $V_{50 \text{ Gy}}$ | 1.64 ± 1.93            | 1.19 ± 1.35   | 0.287   |

(c) Contralateral lung

|                | Free breathing CT plan | MIP based plan | P value |
|----------------|------------------------|----------------|---------|
| $V_{5 \text{ Gy}}$ | 13.65 ± 12.29          | 8.91 ± 20.58  | 0.140   |
| $V_{10 \text{ Gy}}$ | 2.63 ± 4.90            | 1.01 ± 2.08   | 0.160   |
| $V_{20 \text{ Gy}}$ | 0                     | 0              | —       |
| $V_{30 \text{ Gy}}$ | 0                     | 0              | —       |
| $V_{40 \text{ Gy}}$ | 0                     | 0              | —       |
| $V_{50 \text{ Gy}}$ | 0                     | 0              | —       |

*Volume receiving 5 Gy.
†Volume receiving 10 Gy.
‡Volume receiving 20 Gy.
§Volume receiving 30 Gy.
‖Volume receiving 40 Gy.
¶Volume receiving 50 Gy.

($P = 0.034$) for $V_{30 \text{ Gy}}$, 9.18 ± 5.88 cc versus 4.90 ± 3.18 cc ($P = 0.035$) for $V_{40 \text{ Gy}}$, 1.64 ± 1.93 cc versus 1.19 ± 1.35 cc ($P = 0.287$) for $V_{20 \text{ Gy}}$, respectively. There were no significant differences in $V_{30 \text{ Gy}}$ of contralateral lung volume (13.65 ± 12.29 cc in free breathing CT versus 8.91 ± 20.58 cc in 4D MIP CT, $P = 0.140$) and $V_{10 \text{ Gy}}$ (2.63 ± 4.90 cc versus 1.01 ± 2.08 cc, $P = 0.160$) as in Table 3(c).

4. Discussion

The “reproducibility” and “regularity” of respiration are important elements for treating moving tumors influenced by breathing in the 4D era. The RGRT with undefined reproducibility or regularity may result in the decrease of tumor dose and unintentional increase in the surrounding normal tissue. Therefore, it is vital to induce the patient’s respiration as regularly as possible during the 4D RGRT. In addition, breathing is also important for getting quality-guaranteed 4D images with the 4DCT. Various methods to reduce the artifact of the 4DCT and improve quality of the RGRT were introduced during the last ten-year period. As one aspect of it, the audio instruction or the video-guided respiration was reported in several groups of USA and Europe. Kini et al. [15] reported that the RGRT with respiratory training showed improved reproducibility compared to the RGRT without training. Studies comparing the free breathing and the audio-guided breathing revealed that audio instruction provides stable respiratory pattern compared to the free breathing in a limited extent [20, 21]. In addition, Cerviño et al. [22] reported that the visual feedback showed significant benefit to stabilize the respiration for the patients with breast cancer compared to the free breathing. Recent researches on the RGRT using both the audio and the visual guidance demonstrated more meaningful results. The audiovisual feedback system significantly reduced the breathing motion compared to the free or the audio-guided breathing according to George et al. [16]. Crossmann [23] and Goossens et al. [24] also confirmed that the reproducibility was improved by adding the visual component. Thus, most of the studies on the respiratory signals using audio and/or visual devices during RT showed positive results with the device-assisted breathing compared to free breathing. The results of our study were shown to be in accord with these earlier ones with increasing reproducibility and regularity of respiratory amplitude and
period using the complex system-guided breathing. However, the RMSE of breathing period \((0.951 \pm 0.130 \text{ sec}, 0.741 \pm 0.213 \text{ sec}, \text{ and } 0.464 \pm 0.215 \text{ sec for free breathing, audio device-guided breathing, and complex system-guided breathing, resp.})\) was relatively big even for the complex system-guided breathing which might lead to change in phase and amplitude or movement of internal target. In addition, using the RPM system for the RGRT is possible on the assumption that the external motion is synchronized to the movement of the internal organs. Tsunashima et al. [25] analyzed the time difference of the respiratory signals and the three-dimensional tumor movement in 26 patients with lung, liver, and esophageal cancers. According to their report, the variation of the phase was within 0.3 seconds irrespective of organs, and the external signals were well correlated with the internal movement. The synchronism of the external and internal movement was not studied in the present study. Our future studies will follow these considerations. There are several demerits with present study such as a small patient number of 11 and no available data during the real treatment. However, the respiratory signals were collected from two different sessions for 5 minutes each for the three breathing conditions in 11 patients which meant about 1386 signals per the free, the audio-guided, and the complex system-guided breathing. In the latter problem, the actual treatment was done with the complex system-guided breathing and the signals of the free and the audio-guided breathing were not gathered in consideration of delay in the daily treatment time and increase in the workload of staff. Meanwhile, using the RPM system for the RGRT is possible on the assumption that the external motion is synchronized to the movement of the internal organs.

Meanwhile, according to Hau et al. [26], the use of RGRT with audio coaching was not associated with a significant reduction in spinal cord, esophagus, or cardiac dosimetric parameters. However, it did reduce the lung mean dose by 1.33 Gy \((P < 0.001)\) and \(V_{20\text{Gy}}\) by 2.2% \((P < 0.001)\) with gating ranging 85–15% in patients with thoracic malignancies. Another study revealed that RGRT with DBH technique correlated with 32% reduction (19.9% versus 13.5%) in lung \(V_{20\text{Gy}}\) compared to free breathing in patients with esophageal cancer [17]. Our results showed the low dose volume areas of normal liver including \(V_{5\text{Gy}}, V_{10\text{Gy}}, \text{ and } V_{20\text{Gy}}, \text{ and } V_{10\text{Gy}}\) received less doses of radiation with the 4D MIP CT than with the free breathing CT in patients with liver cancer. \(V_{20\text{Gy}}, V_{30\text{Gy}}, \text{ and } V_{40\text{Gy}}\) of ipsilateral lung with plans of 4D MIP CT were significantly favorable than that of the free breathing CT in patients with lung cancer. In spite of relatively wide range of gating (30–70%), the benefit of 4DRT with complex system-guided breathing compared to free breathing was quantified and showed statistical significance.

5. Conclusions

The reproducibility and regularity of respiratory amplitude and period were significantly improved with the complex system-guided breathing compared to free breathing and audio-guided breathing. In addition, the 30–70% gating 4DRT with the complex system-guided breathing was advantageous over free breathing in terms of DVH profiles of normal liver or lung.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] B. Bussels, L. Goethals, M. Feron et al., “Respiration-induced movement of the upper abdominal organs: a pitfall for the three-dimensional conformal radiation treatment of pancreatic cancer,” *Radiotherapy and Oncology*, vol. 68, no. 1, pp. 69–74, 2003.

[2] H. Shirato, Y. Seppenwooleke, K. Kitamura, R. Onimura, and S. Shimizu, “Intrafractional tumor motion: lung and liver,” *Seminars in Radiation Oncology*, vol. 14, no. 1, pp. 10–18, 2004.

[3] G. D. Hugo and M. Rosu, “Advances in 4D radiation therapy for managing respiration: part I—4D imaging,” *Zeitschrift für Medizinische Physik*, vol. 22, no. 4, pp. 258–271, 2012.

[4] R. W. M. Underberg, F. J. Lagerwaard, B. J. Slotman, J. P. Cuijpers, and S. Senan, “Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: an analysis of 4DCT datasets,” *International Journal of Radiation Oncology Biology Physics*, vol. 62, no. 2, pp. 554–560, 2005.

[5] R. George, V. Ramakrishnan, J. V.Siebers, T. D. Chung, and P. J. Keall, “Investigation of patient, tumour and treatment variables affecting residual motion for respiratory-gated radiotherapy,” *Physics in Medicine and Biology*, vol. 51, no. 20, pp. 5305–5319, 2006.

[6] J. A. Purdy, “Current ICRU definitions of volumes: limitations and future directions,” *Seminars in Radiation Oncology*, vol. 14, no. 1, pp. 27–40, 2004.

[7] J. Hanley, M. M. Debois, D. Mah et al., “Deep inspiration breath-hold technique for lung tumors: the potential value of target immobilization and reduced lung density in dose escalation,” *International Journal of Radiation Oncology Biology Physics*, vol. 45, no. 3, pp. 603–611, 1999.

[8] J. W. Wong, M. B. Sharpe, D. A. Jaffray et al., “The use of active breathing control (ABC) to reduce margin for breathing motion,” *International Journal of Radiation Oncology Biology Physics*, vol. 44, no. 4, pp. 911–919, 1999.

[9] P. C. F. Cheung, K. E. Sixel, R. Tirona, and Y. C. Ung, “Reproducibility of lung tumor position and reduction of lung mass within the planning target volume using active breathing control (ABC),” *International Journal of Radiation Oncology Biology Physics*, vol. 57, no. 5, pp. 1437–1442, 2003.

[10] D. Mah, J. Hanley, K. E. Rosenzweig et al., “Technical aspects of the deep inspiration breath-hold technique in the treatment of thoracic cancer,” *International Journal of Radiation Oncology Biology Physics*, vol. 48, no. 4, pp. 1175–1185, 2000.

[11] K. Ohara, T. Okumura, M. Akisada et al., “Irradiation synchronized with respiration gate,” *International Journal of Radiation Oncology Biology Physics*, vol. 17, no. 4, pp. 853–857, 1989.

[12] R. Onimaru, H. Shirato, M. Fujino et al., “The effect of tumor location and respiratory function on tumor movement estimated by real-time tracking radiotherapy (RTRT) system,” *International Journal of Radiation Oncology Biology Physics*, vol. 63, no. 1, pp. 164–169, 2005.
[13] S. Lee, K.-H. Chang, J. B. Shim et al., “Evaluation of mechanical accuracy for couch-based tracking system (CBTS),” *Journal of Applied Clinical Medical Physics*, vol. 13, no. 6, p. 3818, 2012.

[14] Y. Seppenwoolde, R. I. Berbeco, S. Nishioka, H. Shirato, and B. Heijmen, “Accuracy of tumor motion compensation algorithm from a robotic respiratory tracking system: A simulation study,” *Medical Physics*, vol. 34, no. 7, pp. 2774–2784, 2007.

[15] V. R. Kini, S. S. Vedam, P. J. Keall, S. Patil, C. Chen, and R. Mohan, “Patient training in respiratory-gated radiotherapy,” *Medical Dosimetry*, vol. 28, no. 1, pp. 7–11, 2003.

[16] R. George, T. D. Chung, S. S. Vedam et al., “Audio-visual biofeedback for respiratory-gated radiotherapy: impact of audio instruction and audio-visual biofeedback on respiratory-gated radiotherapy,” *International Journal of Radiation Oncology Biology Physics*, vol. 65, no. 3, pp. 924–933, 2006.

[17] F. Lorchel, J. L. Dumas, A. Noé, D. Wolf, J. F. Bosset, and P. Aletti, “Dosimetric consequences of breath-hold respiration in conformal radiotherapy of esophageal cancer,” *Physica Medica*, vol. 22, no. 4, pp. 119–126, 2006.

[18] L. Feuvret, G. Noel, J. J. Mazeron, and P. Bey, “Conformity index: a review,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 64, no. 2, pp. 333–342, 2006.

[19] A. Pyakuryal, W. K. Myint, M. Gopalakrishnan, S. Jang, J. A. Logemann, and B. B. Mittal, “A computational tool for the efficient analysis of dose-volume histograms from radiation therapy treatment plans,” *Journal of Applied Clinical Medical Physics*, vol. 11, no. 1, p. 3013, 2010.

[20] G. F. Persson, D. E. Nygaard, M. Olsen et al., “Can audio coached 4D CT emulate free breathing during the treatment course?” *Acta Oncologica*, vol. 47, no. 7, pp. 1397–1405, 2008.

[21] C. J. A. Haasbeek, F. O. B. Spoelstra, F. J. Lagerwaard et al., “Impact of audio-coaching on the position of lung tumors,” *International Journal of Radiation Oncology Biology Physics*, vol. 71, no. 4, pp. 1118–1123, 2008.

[22] L. I. Cerviño, S. Gupta, M. A. Rose, C. Yashar, and S. B. Jiang, “Using surface imaging and visual coaching to improve the reproducibility and stability of deep-inspiration breath hold for left-breast-cancer radiotherapy,” *Physics in Medicine and Biology*, vol. 54, no. 22, pp. 6853–6865, 2009.

[23] P. H. Cossman, “Video-coaching as biofeedback tool to improve gated treatments: possibilities and limitations,” *Zeitschrift für Medizinische Physik*, vol. 22, no. 3, pp. 224–230, 2012.

[24] S. Goossens, F. Senny, J. A. Lee et al., “Assessment of tumor motion reproducibility with audio-visual coaching through successive 4D CT sessions,” *Journal of Applied Clinical Medical Physics*, vol. 15, p. 4332, 2014.

[25] Y. Tsunashima, T. Sakae, Y. Shioyama et al., “Correlation between the respiratory waveform measured using a respiratory sensor and 3D tumor motion in gated radiotherapy,” *International Journal of Radiation Oncology Biology Physics*, vol. 60, no. 3, pp. 951–958, 2004.

[26] E. Hau, M. Rains, L. Browne, R. Muirhead, and R. Yeghiaian-Alvandi, “Minimal benefit of respiratory-gated radiation therapy in the management of thoracic malignancy,” *Journal of Medical Imaging and Radiation Oncology*, vol. 57, pp. 704–712, 2013.