Respiratory motion management using audio-visual biofeedback for respiratory-gated radiotherapy of synchrotron-based pulsed heavy-ion beam delivery

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Purpose: To efficiently deliver respiratory-gated radiation during synchrotron-based pulsed heavy-ion radiotherapy, a novel respiratory guidance method combining a personalized audio-visual biofeedback (BFB) system, breath hold (BH), and synchrotron-based gating was designed to help patients synchronize their respiratory patterns with synchrotron pulses and to overcome typical limitations such as low efficiency, residual motion, and discomfort.

Methods: In-house software was developed to acquire body surface marker positions and display BFB, gating signals, and real-time beam profiles on a LED screen. Patients were prompted to perform short BHs or short deep breath holds (SDBH) with the aid of BFB following a personalized standard BH/SDBH (stBH/stSDBH) guiding curve or their own representative BH/SDBH (reBH/reSDBH) guiding curve. A practical simulation was performed for a group of 15 volunteers to evaluate the feasibility and effectiveness of this method. Effective dose rates (EDRs), mean absolute errors between the guiding curves and the measured curves, and mean absolute deviations of the measured curves were obtained within 10%–50% duty cycles (DCs) that were synchronized with the synchrotron's flat-top phase.

Results: All maneuvers for an individual volunteer took approximately half an hour, and no one experienced discomfort during the maneuvers. Using the respiratory guidance methods, the magnitude of residual motion was almost ten times less than during nongated irradiation, and increases in the average effective dose rate by factors of 2.39–4.65, 2.39–4.59, 1.73–3.50, and 1.73–3.55 for the stBH, reBH, stSDBH, and reSDBH guiding maneuvers, respectively, were observed in contrast with conventional free breathing-based gated irradiation, depending on the respiratory-gated duty cycle settings.

Conclusions: The proposed respiratory guidance method with personalized BFB was confirmed to be feasible in a group of volunteers. Increased effective dose rate and improved overall treatment precision were observed compared to conventional free breathing-based, respiratory-gated irradiation. Because breathing guidance curves could be established based on the respective average respiratory period and amplitude for each patient, it may be easier for patients to cooperate using this technique. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4897391>]

Key words: heavy ion therapy, respiratory guidance, respiratory gating, audio-visual biofeedback, motion management

1. INTRODUCTION

The major advantage of radiotherapy with charged particles in comparison to photons is improved sparing of healthy tissues due to accurate dose localization in the Bragg peak.¹ Furthermore, heavy charged particles such as carbon ions have a high relative biological effectiveness (RBE) and steep

lateral dose gradients between the target and surrounding tissues due to reduced lateral scattering.^{1–4} However, tumors located in the thoracic and abdominal regions are dynamic and subject to respiratory motion. The interplay between target motion in the tumor and dynamic beam delivery can cause unwanted geometric misses of the target and/or irradiation of normal structures, limiting the normal tissue

sparing potential of heavy-ion radiotherapy.^{5,6} The most precise but also most technically challenging motion mitigation technique is most likely beam tracking,⁷⁻⁹ which is currently under development. Beam gating¹⁰⁻¹³ mitigates target motion directly by irradiating the target during defined motion states only. Also breath-hold (BH)^{14,15} techniques have been widely employed.

Recently, Park *et al.*¹⁶ introduced a novel respiratory motion management method combining a free breathing-based gating technique, the BH technique, and a personalized audio-visual biofeedback (BFB) system.¹⁷⁻²² In this technique, known as “quasibreath-hold (QBH),” a patient is guided to perform short BH repeatedly (without a break) with the aid of an audio-visual BFB process. The amount of residual motion and the number of phase shifts caused by the dynamic property of gating were reduced. In addition, this technique may be better than BH techniques in terms of minimizing the burden of patient cooperation and operator alert. However, all previous studies have been performed using respiratory-gated photon irradiation with linear accelerators delivering continuous beams.

Currently, there are two types of accelerators for particle therapy: the cyclotron and the synchrotron. The cyclotron delivers a nearly continuous beam, as do linear accelerators. Simulating optimal parameters for respiratory-gated radiotherapy

with a cyclotron is relatively simple, and the QBH method proposed by Park *et al.* can be directly translated to this setting. The synchrotron-based heavy-ion accelerator, however, operates in pulse mode at a low repetition rate that is comparable to the patient’s breathing rate. In synchrotron accelerators, energetic heavy ions are usually delivered during a specific portion of the magnet cycle excitation pattern. Each cycle is composed of an acceleration period, a flat-top time during which heavy ions are available for delivery, and a deceleration period, as shown in Fig. 1(a). The spill can be delivered to the target volume only when the respiratory gate-on status is synchronized with the flat-top phase. Efficient delivery of respiratory-gated radiation delivery in such a configuration, therefore, relies on the optimization of the synchronization between the magnet excitation cycle (MEC) and each patient’s respiratory cycle. An error in synchronization can introduce significant inefficiencies in respiratory-gated heavy-ion delivery.

Tsunashima *et al.*²³ have investigated the efficiency of respiratory-gated delivery of synchrotron-based pulsed proton irradiation. In their work, a realistic simulation of the interaction of various accelerator operation parameters and patient respiratory motion parameters was conducted to determine optimal parameters to facilitate efficient delivery of respiratory-gated proton beam irradiation for passively scattered protons generated by a synchrotron. Based on whether the

FIG. 1. Schematic of interactions between respiratory motion and magnetic excitation patterns. A magnet excitation cycle is composed of acceleration, flat top, and deceleration. (a) In conventional respiratory-gated heavy-ion delivery, the beam spill can be delivered to the target volume only when the respiratory gate-on status is synchronized with the flat-top phase. (b) When respiratory patterns are synchronized with the synchrotron’s pattern by prompting the patient to perform short BH, the synchronization error between the magnet excitation and each patient’s respiratory cycle decreases during respiratory-gated heavy-ion delivery.

synchrotron waits in the deceleration phase until the completion of the remainder of the current cycle or not, two modes of synchrotron operation can be distinguished: the fixed cycle and the variable cycle modes. In the fixed cycle mode, all particles have been delivered before normal completion of the flat-top phase, and then the deceleration phase starts. The deceleration phase continues until normal completion of the current cycle in a nonmagnetic excitation status, before initiating the next cycle. They found that corresponding average delivery time was typically three times longer with a fixed MEC pattern with respiratory-gated delivery at a 30% duty cycle (DC) around peak exhalation. However, when a variable MEC was allowed in synchrony with the patient's respiratory cycle, the treatment time only doubled. In another study,²⁴ the same group of investigators indicated that the variable MEC operation mode delivered proton beams more precisely during irregular breathing. The variable MEC pattern has been shown to be an efficient and appropriate synchrotron operation mode that demonstrates flexibility and precision. However, a series of MECs are needed for treatment, and the value of each MEC has to be set prior to the start of delivery for each beam. To maximize the treatment efficiency of a patient using this method, the next respiratory period of the patient must be predicted after the last beam spill but before the start of irradiation with the next spill. The complexity of this process doubled treatment time, although it was still better than a conventional fixed MEC pattern (which was three times longer).

The purpose of this work was to develop a novel technique by combining a personalized audio-visual BFB system, a BH technique, and a synchrotron-based gating technique to help patients synchronize their respiratory patterns with the pulsed synchrotron patterns, as shown in Fig. 1(b). In our technique, a patient is guided to perform short BHs or short deep breath holds (SDBH) with the aid of BFB, following a personalized standard guidance curve or his/her own specific guidance curve (which is acquired by monitoring the patient's normal breathing). Using this technique, the treatment efficiency can be expected to increase, while the amount of residual motion is reduced. Additionally, the burdens of patient cooperation and operator alert can be minimized. To evaluate the feasibility and effectiveness of our method, a practical simulation study was performed in a group of 15 volunteers.

2. MATERIALS AND METHODS

There are two major beam delivery methods in synchrotron-based heavy-ion radiotherapy: passive scattering and spot scanning techniques. This study was conducted based on the passively scattered technique only. Delivery of the prescribed dose for a treatment plan could be achieved by repeating multiple beam spills.

2.A. Accelerator operation patterns

Based on the therapeutic techniques developed at the Heavy Ion Research Facility in Lanzhou (HIRFL), the first hospital-based carbon ion therapy facility (Heavy Ion Medical Machine,

HIMM) has been designed. This facility is currently under construction in Lanzhou, China. The HIMM facility principally consists of a synchrotron as the main accelerator, a cyclotron as the injector, and four treatment rooms.

The synchrotron employs the RF-knockout slow extraction method to extract beams.²⁵ The durations of acceleration and deceleration are constant (1.6 s each) and cannot be modified by the operator, regardless of beam energy. The duration of the flat-top phase can be varied between 1 and 10 s, during which carbon ions are available for delivery. The MEC is an operator-selected value (4.2–13.2 s) that can be set prior to the delivery of each beam. Once set, this value cannot be changed until the completion of delivery of that beam. As far as the HIMM facility is concerned, the shortest possible duration of MEC is 4.2 s (acceleration = 1.6 s, deceleration = 1.6 s, and flat top = 1.0 s), offering the fastest treatment delivery time and maximum effective dose rate (EDR) in nongated delivery mode.

In this study, the beam intensity was assumed to deliver a dose of 30 mGy per beam spill, which is a moderate value designed for various energy beams in the HIMM facility. The RF-knockout method was applied to resonantly extract the beam from the synchrotron at the HIMM complex. During beam extraction, a feedback system was introduced to modify the time structure of the beam and to suppress rippling and instability.²⁵ The shape of the beam spills was supposed to be kept consistent throughout beam delivery.

2.B. In-house software program for analysis and audio-visual biofeedback control

Patients' respiratory tracings were recorded using a commercially available laser displacement sensor (ILD1700, MICRO-EPSILON®, Germany). Continuous position readings corresponding to respiration were analyzed and stored at 30 samples/s. The patients' respiratory tracings were shown on a LED monitor beside them, facilitating visual BFB. Together with the laser displacement sensor, the LED monitor, a speaker, and a computer, an audio-visual BFB system was constituted. Corresponding software was built with MATLAB 7.10 (MathWorks®, Massachusetts) to control the system and perform the audio-visual BFB process. Major functions of the software are as follows: (1) body surface marker position acquisition and real-time processing, (2) establishing a personalized respiration mode, (3) setting gating parameters, (4) displaying visual BFB on the LED monitor, (5) displaying gating signals and real-time beam profiles on the LED monitor, and (6) saving log files containing the marker positions in time sequence.

Two curves are displayed on the screen; one is a breathing curve indicating a patient's current breathing pattern, and the other is a guidance curve based on a personalized respiration model derived from each patient to help them keep their breathing pattern as consistent as possible. In addition to this visual BFB, the audio prompts based on the visual guiding curve are available through the speaker in the treatment room. A schematic representation of the setup is illustrated in Fig. 2.

FIG. 2. Setup for the audio-visual BFB system. The in-house software processes the patient's abdominal surface marker positions, which are acquired by a laser displacement sensor in real-time, and shows the patient's breathing trace together with the guidance curve on the LED screen. Meanwhile, the gate signal and synchrotron operation patterns are also displayed on the LED screen to make it easy for patients to synchronize their respiratory pattern with the synchrotron operation pattern.

In this study, abdominal surface motion was assumed to be mainly in the vertical direction, and the respiratory signal acquired was the anterior–posterior motion of a marker block placed on the abdomen of the patient between the umbilicus and the xiphoid.

2.C. Personalized modeling of guidance curves

The method used in this study to generate the personalized respiration model was similar to the moderate BH one proposed by Park *et al.*¹⁶ Furthermore, to synchronize respiratory patterns with synchrotron operation, the accelerator's operation pattern has to be taken into account. As described in Sec. 2.A, the durations of acceleration and deceleration are constant (1.6 s each) and cannot be modified by the operator. We also investigated the SDBH method in comparison with the BH to identify the optimal combination of respiration and synchrotron patterns.

The strategy of the model construction method is illustrated in Fig. 3. First, the modeling procedure begins by obtaining patient free breathing (FB) and deep inspiration breathing (DIB) samples from four to six respiration cycles, respectively. Depending on the average period, amplitude, and the end-expiration phase duration measured during FB, a FB model based on a $\cos^2$, $\cos^4$, or $\cos^6$ curve is acquired.^{26,27}

Second, the type of synchronization between the respiration and synchrotron patterns is determined. If the average respiration period is equal to or greater than 3.2 s, one cycle of the FB model is set between two successive flat tops. Otherwise, two successive cycles of the FB model are set. In this way, the fastest treatment delivery time and maximum effective dose rate in the breath-guided delivery mode can be obtained because the time duration between two successive flat tops is at least 3.2 s (acceleration = 1.6 s and deceleration = 1.6 s), and the respiratory period is generally greater than 1.6 s. Because the FB model is precisely established on the basis of the average respiratory period and amplitude for each patient, patient cooperation becomes easier.

Finally, the standard BH (stBH) model is established in two steps. First, a constant BH signal of 1.0 s in length is added to the end-point of the FB model, and then the one-cycle guidance curve is duplicated. Meanwhile, the synchrotron's operation pattern is determined according to the flat-top time of 1.0 s and the average respiratory period. Patients are instructed to breathe following their own stBH guiding curve and control their breath by watching the on-screen instructions. Furthermore, to examine whether following the stBH guiding curve is easy for each patient (because this curve does not reflect the patient's actual breathing wave), a cycle of the patient's respiration trace during the stBH guidance process is also recorded as a representative BH (reBH) guidance curve, allowing the patient to follow the reBH guidance curve more easily.

Using the same procedure as described above, the standard SDBH (stSDBH) and representative SDBH (reSDBH) models are constructed.

2.D. Simulation study with volunteers

Fifteen healthy volunteers (nine males and six females) took part in the simulation study. Of these, three volunteers were medical physicists, three were graduate students, and nine were members of the general public. The group had a wide age range (from 23 to 43 yr), as well as a wide range of weights (from 53 to 95 kg). A total of 90 5-min breathing traces of the volunteers' respiratory motions were collected using the various types of BFB.

Prior to the simulation, each volunteer underwent a training session to familiarize him/her with the BFB interface and train him/her in the respiratory maneuvers to be tested. One week later, the actual simulation was performed. The volunteers were initially asked to breathe normally (called a FB session) and then deeply (called a DIB session) without any instruction or feedback. Each session lasted for 5 min, and the breathing signal data were recorded for future use. Based on the average respiratory period and the amplitude measurements

FIG. 3. A flow chart illustrating how to establish a personalized stBH model from sample patient respiration data during FB. A FB model was generated from the FB samples based on a $\cos^2$, $\cos^4$, or $\cos^6$ curve. Depending on whether the respiration period was greater or less than 3.2 s, two different synchronization types were determined between the respiration and synchrotron patterns. The stBH model was then established by inserting a constant BH signal with a length of 1.0 s into the end-point of the FB model.

derived from the FB and DIB sessions, the stBH and stSDBH models were determined. Inspiratory, breath-hold, and expiratory instructions were given, and the subsequent breathing data were recorded again for 5 min each with BFB instruction, following the respective guidance curves of the stBH and stSDBH models. Once the standard model guiding sessions were completed, the reBH and reSDBH models were determined and displayed on the LED screen to guide the volunteers' breathing with the guidance of their own respiratory patterns. Successive breathing data were also recorded for 5 min for both the reBH and reSDBH guidance sessions. In addition to this visual biofeedback, the volunteers were given audio instructions to reinforce the visual guidance.

Each simulation was performed in the treatment room, as shown in Fig. 2. The laser displacement sensor was placed just above the abdomen. All five maneuvers for each volunteer took approximately half an hour; no volunteer experienced discomfort during the maneuvers.

2.E. Determination of gating parameters

For comparison purposes, the simulation study was designed to determine the optimal beam delivery that would result in the most efficient delivery for conventional FB-based respiratory-gated pulsed heavy-ion irradiation. The preselected threshold level for gating was set on each volunteer's FB curve, and the gating signal was superimposed onto the synchrotron MEC pattern to examine the effects of each parameter on the overall treatment delivery time and the amount of residual motion. As a reference set, the fastest delivery should be the non-gated beam irradiation with a MEC of 4.2 s for the passive scattering mode.

Three parameters may affect the final result.²³ In the present simulation study, the effect of start phase correlation between respiration and synchrotron magnet excitation was simulated for four initial respiratory phase values: $\pi/2$, π , $3\pi/2$, and 2π . The effects of synchrotron MEC for respiratory-gated

irradiation were examined with various MEC settings of 4.2, 5.2, 6.2, 7.2, 8.2, 9.2, 10.2, 11.2, 12.2, and 13.2 s. The DC values for respiratory-gated irradiation were set to 10%, 20%, 30%, 40%, and 50% around the peak exhalation phase of the respiratory cycle for each volunteer's respiratory motion data.

2.F. Analysis of treatment efficiency and motion uncertainty

A total of 90 respiration log files was analyzed to determine the following: (1) the EDR for respiratory-gated delivery with BFB and FB based on different parameter settings and for nongated delivery; (2) how well the volunteers were able to perform the stBH, reBH, stSDBH, and reSDBH maneuvers; (3) to what extent the stBH, reBH, stSDBH, and reSDBH maneuvers reduced residual motion compared to the conventional FB-based respiratory-gated beam delivery. To evaluate the EDR, the dose delivered to the target volume only when the respiratory gate-on status was synchronized with the synchrotron flat-top phase was accumulated during the 5 min simulation process for each respiratory maneuver. Thus, the EDR was calculated by dividing the accumulated dose by the time duration of 5 min.

To answer the second question, a parameter for compliance evaluation, mean absolute error (MAE) between the guiding and measured respiration curve, was used. This parameter was described by Park *et al.*¹⁶ as follows:

Mean absolute error (MAE)

$$= \frac{1}{N} \sum_{i=1}^N |z_{\text{measured}}(t_i) - z_{\text{guide}}(t_i)|, \quad (1)$$

where t_i is the i th time point sampled within the DC that was synchronized with the synchrotron flat-top phase, N is the total number of sampled time points, $z_{\text{guide}}(t_i)$ is the position of the guiding curve at t_i , and $z_{\text{measured}}(t_i)$ is the position of the measured curve at t_i .

The residual motion was evaluated with mean absolute deviation (MAD) given by

Mean absolute deviation (MAD)

$$= \frac{1}{N} \sum_{i=1}^N |z_{\text{measured}}(t_i) - \bar{z}_{\text{measured}}|, \quad (2)$$

where $\bar{z}_{\text{measured}}$ is the mean position of the measured curve within the DC synchronized with the synchrotron flat-top phase.

3. RESULTS

The EDR with a MEC of 4.2 s for nongated situations was found to be 0.432 Gy/min. This value was treated as a reference result for comparison. For the gated cases, any error in synchronization between respiratory gate-on status and the flat-top phase could introduce significant inefficiencies in respiratory-gated delivery, and the EDRs would decrease compared to the reference value mentioned above.

3.A. Effect of the start of the respiratory phase and synchrotron magnet excitation cycle as well as the respiratory gate duty cycle on conventional, free breathing-based, respiratory-gated, pulsed heavy-ion irradiation

Figure 4 illustrates the distribution of EDR of FB-based gating depending on various MEC and DC settings, based on 3000 statistical data points that were obtained from the 15 volunteers; the error bars show the standard deviations (SDs) accounting for the initial phase effect from $\pi/2$ to 2π for the total breathing traces.

In general, the average EDR of the gated irradiation gradually decreased as the MEC increased from 4.2 to 13.2 s and was 1.73–11.09 times less than with nongated beam delivery, depending on the DC settings. Figure 4 also shows that variations in the initial phase of respiratory motion tended to have a greater influence (the error bar was longer) on the EDR with shorter DC settings; this influence gradually decreased when the MEC increased from 4.2 to 13.2 s.

3.B. Treatment efficiency using the audio-visual biofeedback system

Figure 5 shows the distribution of the EDRs of the nongated, the FB-based respiratory-gated, and the breathing-guided treatments using BFB instructions and following the guidance curves of the stBH, reBH, stSDBH, and reSDBH models with different DC settings, using the 90 respiratory motion traces from the 15 volunteers. For FB-based gating, the histogram represents the overall EDR while taking into account the effect of the initial respiratory phase and MEC at the different DC levels.

In general, the EDR for the nongated irradiation was 3.13–6.56 times greater than the overall EDR for the FB-based gated radiation, depending on the DC settings. Moreover, it was

Fig. 4. Effect of the initial respiratory phase and synchrotron MEC as well as respiratory-gated DC on conventional FB-based, respiratory-gated, pulsed heavy-ion irradiation. The error bars represent the SDs, accounting for the start phase effects of the initial total breathing traces from $\pi/2$ to 2π at various MECs with DC levels of 10%, 20%, 30%, 40%, and 50%.

FIG. 5. Overall results for average effective dose rate in nongated heavy-ion irradiation, respiratory-guided irradiation with BFB instructions following the guidance curves of the stBH, reBH, stSDBH, and reSDBH models with various DC settings, and FB-based, respiratory-gated, heavy-ion radiation, accounting for the effect of the initial respiratory phase and MEC at the different DC levels. The box plots represent one standard deviation, and the bands in the boxes are the medians. The extremes are the maximum and minimum values for each data set. Student's *t*-test, * $p < 0.05$, ** $p < 0.01$ versus FB-based gating irradiation for each DC.

1.31–1.41, 1.31–1.43, 1.81–1.87, and 1.81–1.85 times greater than the average EDRs for the stBH, reBH, stSDBH, and reSDBH guiding maneuvers, respectively. These results indicate the EDRs in the breathing guiding maneuvers improved (Student's *t*-test, $p < 0.01$ for all respiratory-guided maneuvers for each DC) compared to those using FB-based gated radiation. This was achieved by synchronizing respiration with the synchrotron's operation patterns, as shown in Fig. 1. Because synchronization between the MEC and each patient's respiratory cycle improved during respiratory-gated beam delivery, the corresponding treatment efficiency increased naturally.

Generally, the overall EDR for the FB-based gating gradually increased with the DC varying from 10% to 50%. However, it remained almost constant for the stBH, reBH, stSDBH, and reSDBH guiding maneuvers. There was almost no difference in average EDR between the stBH and reBH maneuvers, as well as between the stSDBH and reSDBH ones. However, the treatment efficiency of BH-based guidance seemed to be higher than SDBH-based guidance because the average respiratory period of DIB was generally longer than that of FB, leading to a longer MEC for synchronization. The simulated treatment time required to deliver a prescribed dose of 1 Gy for each maneuver is graphically shown in Fig. 6. Clearly, the stBH and reBH guiding methods had the highest treatment efficiencies of all respiratory-gated delivery settings.

Interestingly, there were two special cases among the 15 volunteers. Figure 7(a) shows a typical example of a log acquired from a reBH guiding simulation with a FB period of 3.5 s. The virtually generated synchrotron signals were perfectly matched with the personalized guiding curve cycle by cycle. However, one out of the volunteers presented a different

situation, with a FB period of 2.9 s, as shown in Fig. 7(b). To coordinate the synchrotron operation with respiratory patterns, the duration between two successive synchrotron flat tops had to be set to 5.8 s. Thus, the final MEC was 6.8 s (plus a BH duration of 1.0 s). However, the volunteer's DIB period was 4.1 s (greater than the boundary of 3.2 s), as shown in Fig. 7(c). Thus, the MEC was determined to be 5.1 s when using the stSDBH/reSDBH guidance maneuvers. In other words, the treatment efficiency was higher for stSDBH/reSDBH than for stBH/reBH guidance maneuvers for this volunteer. An opposite case that occurred during the simulation study is shown in Fig. 7(d), where the volunteer's FB period was 2.3 s (less than the boundary of 3.2 s). In this case, the MEC was determined to be 5.6 s (two FB periods plus a BH time duration of 1.0 s). However, the volunteer's DIB period was 6.2 s, as shown in Fig. 7(e). Thus, the final MEC had to be set to 7.2 s. The treatment efficiency, therefore, was higher for the stBH/reBH than for stSDBH/reSDBH guidance maneuvers for this volunteer. These were two special cases during the simulation process and will need to be considered in actual clinical circumstances.

3.C. Evaluation of motion uncertainty

Figure 8 displays the histogram of the MAE values that were derived from all maneuvers at the various DC levels. The average values of the MAEs at the 30% DC were 0.27 ± 0.07 , 0.28 ± 0.07 , 0.31 ± 0.13 , and 0.35 ± 0.13 mm for the stBH, reBH, stSDBH, and reSDBH maneuvers, respectively. In general, the MAE results demonstrated that the volunteers could comply with the stBH and reBH maneuvers better than with the stSDBH and reSDBH maneuvers; there was almost no difference in MAE distributions between all gate threshold levels. It may have been difficult for the volunteers to control their DIB when they were guided to perform short BH following the guidance curves. In addition, there was better compliance when guidance with the standard model (stBH or

FIG. 6. Simulated treatment times to deliver a prescribed dose of 1 Gy for each maneuver. Using stBH and reBH guidance, a significant reduction in treatment time compared to the gating maneuver was observed.

FIG. 7. Examples of the logs acquired from the simulation of the reBH and reSDBH guiding maneuvers. (a) The FB period (≈ 3.5 s) was greater than 3.2 s, and the virtually generated synchrotron signals were matched with the personalized guidance curve cycle by cycle. (b) The FB period (≈ 2.9 s) was less than 3.2 s, and two successive cycles of the FB model were set between two successive flat tops. The final MEC was therefore determined to be 6.8 s (two FB periods plus a BH duration of 1.0 s), which was larger than 5.1 s (one DIB period of 4.1 s plus a BH time duration of 1.0 s) for the reSDBH guiding maneuver (c). (d) The FB period (≈ 2.3 s) was less than 3.2 s, and the MEC was determined to be 5.6 s (two FB periods plus a BH time duration of 1.0 s), which was less than 7.2 s (one DIB period of 6.2 s plus a BH time duration of 1.0 s) for the reSDBH guiding maneuver (e).

FIG. 8. Values of the MAE for each threshold level of 10% DC, 20% DC, 30% DC, 40% DC and 50% DC for each maneuver. The error bars represent one standard deviation. There was almost no difference in the MAE distributions over all gate threshold levels, and the volunteers were able to comply with the stBH and reBH maneuvers better than with the stSDBH and reSDBH maneuvers.

stSDBH) was used, compared with the representative model (reBH or reSDBH).

Figure 9 shows the distribution of the MADs of the non-gated, the FB-based respiratory-gated, and respiratory-guided radiation techniques using BFB instruction and following the guidance curves of the stBH, reBH, stSDBH, and reSDBH models with different DC settings. The average MAD values were 2.40 ± 1.01 , 0.36 ± 0.08 , 0.53 ± 0.12 , 0.71 ± 0.17 , 0.90 ± 0.23 , and 1.10 ± 0.30 mm for nongated radiation and FB-based gating at the threshold levels of 10% DC, 20% DC, 30% DC, 40% DC, and 50% DC, respectively. The magnitude of residual motion for the FB-based gating was 2.18–6.67 times less than the nongated irradiation, depending on the DC settings. The average values of the MADs in the 30% DC were 0.27 ± 0.08 , 0.24 ± 0.06 , 0.26 ± 0.08 , and 0.27 ± 0.10 mm for the stBH, reBH, stSDBH, and reSDBH maneuvers, respectively. There was almost no difference in MAD distribution between the stBH, reBH, stSDBH, and reSDBH maneuvers at all gate threshold levels, which was very similar to the distribution of the MAE values. The magnitude of residual motion for the respiratory-guided methods was almost ten times less than that of nongated radiation, regardless of the DC settings. The MAD results demonstrate that the respiratory-guided maneuvers improved the overall treatment precision (Student's *t*-test, $p < 0.01$ for all respiratory-guided maneuvers for each DC) compared to FB-based gated radiation.

To investigate whether there was any difference in the effectiveness of the technique between volunteers who were members of the staff (six people) versus the general public (nine people), the data for each volunteer group were analyzed separately. No obvious difference between these two groups was found. This result favorably supports the potential use of these respiratory-guided methods in actual patients.

FIG. 9. Values of the MAD for nongated heavy-ion radiation, respiratory-guided radiation with BFB instruction following the guidance curve of the stBH, reBH, stSDBH, and reSDBH models with different DC settings, and FB-based, respiratory-gated, heavy-ion radiation, accounting for the effect of the start phase and MEC for each gating threshold level in the DC. The error bars represent one standard deviation. The respiratory-guided methods showed obvious improvement in the overall treatment precision of respiratory-gated heavy-ion irradiation compared to the conventional FB-based gating method. Student's *t*-test, * $p < 0.05$, ** $p < 0.01$ versus FB-based gating irradiation for each DC.

4. DISCUSSION

A respiratory guidance method that combines a personalized audio-visual BFB system, a BH technique, and a synchrotron-based gating technique is introduced in this work with the goal of helping patients to synchronize their respiration with the synchrotron's operation patterns. This technique is expected to increase treatment efficiency while reducing residual motion. Although this simulation work was performed in conjunction with heavy-ion radiotherapy, the respiratory guidance method is also applicable to the analogous method of synchrotron-based proton therapy. The present study is, to the best of our knowledge, the first trial in volunteers to test the feasibility of synchronizing respiratory patterns with synchrotron patterns by prompting participants to perform short BH according to personalized optimal guiding curves with the aid of BFB.

To this end, in-house simulation software was designed to control the BFB system. This software performed the following major functions: acquisition and real-time processing of body surface marker position, establishing personalized respiration models, setting gating parameters, displaying visual BFB and gating signals as well as real-time beam profiles on a LED monitor, and saving log files that contain the marker positions in time sequence. Ninety respiratory motion traces from 15 volunteers were analyzed in this simulation study.

Our results indicate that respiratory guidance methods improve the overall efficiency of respiratory-gated heavy-ion radiation. For FB-based, respiratory-gated radiation, the overall beam delivery time was 3.13–6.56 times longer than for the nongated radiation, accounting for the effects of the initial

respiratory phase and MEC, depending on the DC settings. With respiratory guidance methods, beam delivery time decreased by factors of 1.31–1.41, 1.31–1.43, 1.81–1.87, and 1.81–1.85 for the stBH, reBH, stSDBH, and reSDBH guidance maneuvers, respectively. One could expect an increase in average EDR by factors of 2.39–4.65, 2.39–4.59, 1.73–3.50, and 1.73–3.55 for the stBH, reBH, stSDBH, and reSDBH guidance maneuvers, in comparison with conventional FB-based respiratory-gated radiation, depending on the DC settings. These results are notably better than those presented by Tsunashima *et al.*²³ Thus, respiratory-gated irradiation of synchrotron-based pulsed heavy-ion irradiation is feasible and more efficient when the respiratory guidance methods proposed in this work are used.

Furthermore, beam delivery with respiratory guidance has the advantages of less uncertainty and better reproducibility. The magnitude of residual motion for FB-based gating was 2.18–6.67 times less than nongated radiation, according to the DC settings. However, the magnitude of residual motion for the respiratory guidance methods was almost ten times less than observed during nongated radiation and did not depend on the DC settings, suggesting that the respiratory guidance methods improved the overall treatment precision of respiratory-gated heavy-ion radiation.

This study hypothesized that guiding the external respiration signal would help regulate the internal target position. Because such an external signal does not accurately represent the internal tumor motion, the accuracy of this technique is limited by the correlation of the external marker with the target. Although beam-to-beam and day-to-day variations in this correlation have been observed in a study by Berbeco *et al.*,²⁸ results from previous work examining the correlation between external respiratory motion signals and internal tumor motion have indicated that external signals can be used as reasonable surrogates for internal motion for both FB-gated^{29–31} and BH (Refs. 14, 19, and 32) techniques. Another observation from similar correlation studies has been the presence of a phase difference between external and internal motions.³³ The phase difference between external respiratory motion and internal tumor motion has been reported in the literature to be on the order of 0.3 s.³⁴ However, to focus the aim of this study on evaluating the efficacy of the respiratory guidance methods, we used external marker motion only.

One of the limitations of our study is the use of healthy volunteers rather than patients. The volunteers were younger than most patients and their overall health and lung function were presumably better. This may not give a realistic indication of the performance of the reported technique in clinical scenarios. Therefore, potential candidates for this technique may be patients with breast, pancreas, or liver cancers, who generally have good lung function.¹⁶ Furthermore, more training sessions may be needed to increase reproducibility of breathing during each treatment session, as patients relax and their breathing is less forced.²¹ To implement respiratory guidance methods into routine clinical practice, some technical improvements, such as the integration of the audio-visual BFB system into the treatment control system, are required.

Another limitation is that the volunteers only performed one session. Typically, radiotherapy lasts for several sessions, each of which may be longer than 5 min. To estimate the session-to-session variations and longer performance of the respiratory guidance methods proposed in this work, we have already carried out another simulation that uses a treatment plan with a prescribed dose of 2 Gy per fraction. For this study, four sessions were chosen to evaluate the reproducibility of subject compliance with the respiratory guidance maneuvers in different sessions. For each volunteer subject, the plan was virtually delivered three times using the different respiratory guidance maneuvers (stBH/stSDBH, reBH/reSDBH, and FB-based gating with a MEC of 4.2 s) for each treatment session. No obvious variations in treatment time and MAD values in the different sessions were observed for any of the maneuvers compared to the results obtained in this work. These data will be presented in a separate publication. Therefore, a single 5-min session can test these respiratory guidance techniques and provide a good estimate for clinical scenarios.

The present study focused on respiratory gating that was used only in the context of a passively scattered heavy-ion delivery technique. However, it is likely that most particle therapy centers prefer to perform scanned beam techniques due to the increased conformity of the applied dose distribution at the target and the avoidance of patient-specific compensators. Gating and beam tracking are available techniques for motion management in scanned beam settings. Although the technical feasibility of beam tracking has been demonstrated already, precise motion monitoring of the target is required for clinical implementation. Furthermore, more knowledge regarding the validity of motion compensation parameters between treatment fractions and their adaptation needs to be obtained.³⁵ However, for gated radiotherapy using the respiratory guidance methods proposed in this work, the interplay effects between dynamic beam delivery and target motion could be largely reduced because of the small residual movement, suggesting that these respiratory guidance methods are also applicable to respiratory-gated delivery of heavy-ion radiation in the spot scanning mode. This will be the subject of future study.

5. CONCLUSIONS

We developed a novel respiratory guidance method by combining a personalized audio-visual BFB system, a BH technique, and a synchrotron-based gating technique to help patients synchronize their respirations with a synchrotron's operation patterns. A practical simulation study conducted with 15 volunteers demonstrated the feasibility of this method by showing an increase in the overall EDR by a factor of 1.73–4.65 compared to conventional FB-based respiratory-gated radiation. The magnitude of residual motion for the respiratory guidance method was almost ten times lower than for nongated radiation. This technique may facilitate patient cooperation, as a respiratory guidance curve can be established based on the respective average respiratory period and amplitude for each patient.

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