Residual motion of lung tumors in end-of-inhale respiratory gated radiotherapy based on external surrogates

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It has been noted that some lung tumors exhibit large periodic motion due to respiration. To limit the amount of dose to healthy lung tissues, many clinics have begun gating radiotherapy treatment using externally placed surrogates. It has been observed by several institutions that the end-of-exhale (EOE) tumor position is more reproducible than other phases of the breathing cycle, so the gating window is often set there. From a treatment planning perspective, end-of-inhale (EOI) phase might be preferred for gating because the expanded lungs will further decrease the healthy tissue within the treatment field. We simulate gated treatment at the EOI phase, using a set of recently measured internal/external anatomy patient data. This paper attempts to answer three questions: (1) How much is the tumor residual motion when we use an external surrogate gating window at EOI? (2) How could we reduce the residual motion in the EOI gating window? (3) Is there a preference for amplitude- versus phase-based gating at EOI? We found that under free breathing conditions the residual motion of the tumors is much larger for EOI phase than for EOE phase. The mean values of residual motion at EOI were found to be 2.2 and 2.7 mm for amplitude- and phase-based gating, respectively, and, at EOE, 1.0 and 1.2 mm for amplitude- and phase-based gating, respectively. However, we note that the residual motion in the EOI gating window is correlated well with the reproducibility of the external surface position in the EOI phase. Using the results of a published breath-coaching study, we deduce that the residual motion of a lung tumor at EOI would approach that at EOE, with the same duty cycle (30%), under breath-coaching conditions. Additionally, we found that under these same conditions, phase-based gating approaches the same residual motion as amplitude-based gating, going from a 28% difference to 11%, for the patient with the largest difference between the two gating modalities. We conclude that it is feasible to achieve the same reproducibility of tumor location at EOI as at EOE if breath coaching is implemented, enabling us to reap the benefits of the dosimetric advantage of EOI gating. © 2006 American Association of Physicists in Medicine. [DOI: 10.1118/1.2358197]

Key words: radiotherapy, gating, residual motion, organ motion, breath coaching

I. INTRODUCTION

In external beam radiotherapy, there is a dosimetric advantage to treating a lung patient at inspiration. To this end, clinics have used breath hold techniques such as deep-inspiration breath hold (DIBH) to reduce lung toxicity. However, DIBH may not be suitable for lung cancer patients who have compromised pulmonary function. For these patients, it may still be beneficial to use gated radiotherapy under normal breathing conditions (i.e., not deep-inspiration) at end-of-inhale (EOI), as opposed to end-of-exhale (EOE).

During normal breathing, total lung volume can increase by 12%–40% (mean: 22%) at inhalation. Of course, the actual amount is highly patient dependent. A corollary to the increase in lung volume at inspiration is the decrease in physical density of the lung. Lung density is not only a function of breathing phase but also gender, age, and location (among other things). Compiling a set of categorical measurements of lung density at different breathing phases is difficult because of all of these factors. Fujisaki et al. found the average lung density at “shallow inspiration,” “shallow expiration,” and free-breathing to be 0.17, 0.23 g/cc, and 0.22 g/cc, respectively. However, it is unclear how “shallow inspiration” is defined in that work.

A recent study by Biancia et al. has shown that there is a “minor” dosimetric benefit to gating at normal EOI (i.e., without a deep breath-hold maneuver) for the ten patients...
studied. In general, a treatment beam of the same aperture irradiates less healthy lung tissue with the patient at inhale than at exhale. Exactly how much is spared depends on the location of the tumor as well as age, gender, pulmonary ability, and other physiological patient-specific factors. Biancia et al. based their results on the lungs as the only limiting structure in dose escalation (dose to the spinal cord was calculated but not taken into account for dose escalation, the esophagus was not taken into account at all). They report that the average maximum prescription dose—with the constraint that NTCP $\leq 25\%$—is 89.6 Gy for EOE and 94 Gy for EOI. However, half of the patients studied show an absolute difference in maximum prescription dose less than 3.5%, while the other half ranges from 8% to 15.6% (mean: 12.5%), all in favor of EOI gating. For the five patients that showed a strong dosimetric benefit with EOI gating, the maximum prescription dose—with the constraint that NTCP $\leq 25\%$—is 76.6 Gy for EOE and 86.2 Gy for EOI. In a recently published, large population study, it was reported that 5 year local control rates increase approximately 1.3% for every 1 Gy delivered above 70 Gy ($R^2=0.981$). From the results of that study, we can deduce that, on average, for the patients studied by Biancia et al., the 5 year local control rates would increase from 44.5% to 50.1% if EOI gating were used instead of EOE. For the half of the patients that showed the most benefit from EOI gating, the 5 year local control rates would increase from 28.0% to 40.2%, with the greatest advantage for one patient being an increase of 29.8% to 45.1%. These numbers clearly show that the dosimetric benefit of EOI gating is patient dependent and the increase in local control versus EOE gating can be significant.

A drawback to EOI gating that has been noted in previous publications is that the amplitude of EOE is more reproducible than EOI. This would seem to make EOE phase safer and less time consuming for clinical respiratory gating, although the irradiation occurs when the lungs are in their densest state. The present study was performed with the intention of determining whether the large external surrogate residual motion at EOI translates into large tumor residual motion, and, if so, whether abatement of the motion is possible by increasing the reproducibility of the external marker at EOI. We investigated the possibility of reducing the tumor residual motion at EOI to the level of EOE. Our goal is to explore a gating scheme that combines the dosimetric advantages of EOI irradiation with the better reproducibility of EOE.

This is not a treatment planning study. This is a study of the tumor position, not its geometry or the relative geometries of adjacent structures. Ideally, this investigation would include true four-dimensional volumetric data to analyze the delivered dose for an entire course of treatment, but that is not technically feasible at this time. Therefore, this inquiry is purely an analysis of the precision of a gating technique.

**II. METHODS AND MATERIALS**

**A. External and internal gating systems**

The Radiation Oncology clinic at the Nippon Telegraph and Telephone Corporation (NTT) Hospital in Sapporo, Japan, is equipped with a Mitsubishi Real-time Radiation Therapy (RTRT) system. Patients with abdominal and thoracic tumors, treated with this system, typically have two to four 1.5 mm diameter gold ball-bearings (bb’s) implanted in or near the tumor. During treatment, one of these radio-opaque markers is tracked in real-time with stereoscopic diagnostic x-ray fluoroscopy, and the treatment beam is turned on when the marker is within a predetermined 3D window. An external surrogate gating system was installed and integrated with the RTRT system by Mitsubishi (see Fig. 1). The AZ-733V “RespGate” external respiratory gating system (Anzai Medical, Tokyo, Japan) monitors the movement of the patient’s abdominal surface by a laser displacement sensor. This gives a relative measurement of the distance from the laser housing to the abdomen. The signal from the surface monitor is synchronized with the signal from the fluoroscopic unit so that the log files contain the three-dimensional marker position and the external surface position at every time point [see Fig. 2(a) and 2(b)]. The rate of data acquisition for this entire system is 30 frames per second. Note that the fluoroscopic and laser measurements are taken even when the treatment beam is gated off. We are extracting continuous data while the treatment, itself, is gated. We use the internal/external correlated data to perform simulations of external gating scenarios (like the study presented here). The imaging is performed throughout each treatment, so we were able to obtain large statistics. This is the only dataset that has been published with synchronized 3D tumor location and 1D abdominal position for complete treatments of multiple lung patients.
B. The patients

A total of eight lung patients were studied. The details of each patient are given in Table I. Data were taken for only a single day for patients 1–3; because no radiotherapy treatment was given to these patients at the NTT hospital, they were brought in to test the feasibility of the system. Patients 4–8 were treated with 40–48 Gy in 4–8 fractions. All of patients in this analysis have internal marker motion greater than 1 cm peak-to-peak. Patient 5 was treated twice, 2 months apart. Since the same site was treated and no isocenter shift was made, we used both sets of data in the evaluation, under the same patient name. Some beams/days were brought in to test the feasibility of the system. Patients 5 were treated twice, 2 months apart. Since the same site was treated and no isocenter shift was made, we used both sets of data in the evaluation, under the same patient name. Some beams/days were excluded because the patient shifted during treatment.

In this study, the patients were not coached during their treatments. The resulting data are considered “free-breathing” and a good representation of how patients can change their breathing while on the treatment couch if they are not coached.

C. Patient setup

In the CT simulation session, a scan is taken with the patient’s breath held at EOE. At each treatment session, patients are initially set up to skin marks using in-room lasers. Short fluoroscopic imaging sessions are performed to determine the position of the markers at the EOE phase. The 3D marker position is compared to the planned position. The RTRT system then calculates the appropriate couch shift (performed by the therapist) to bring the target to isocenter. The physician monitors the fluoroscopy to verify that the markers are properly tracked and can reach the internal gating window at EOE. This internal fiducial-based setup procedure eliminates the daily setup error (interfractional variations). Any positional errors occurring during the treatment are then due to intrafractional variations. This is a very important point: because the patient is setup based on the fiducial marker position (tumor-based setup versus bony anatomy-based setup) there is essentially no setup error. A complete description of the treatment procedure has been given by Shirato et al.14

D. Data analysis

The data acquired by both the internal and external monitoring systems indicate a “position” at each time step. For the external monitoring system, position is the distance from the abdominal surface to the laser housing. In the internal monitoring system, the position of the tracked marker is calculated in isocenter coordinates. The internal marker position and external surface displacement are written to a logfile that is exported for off-line evaluation. To calculate the phase of the external signal for each time point, a retrospective algorithm is employed.15 The EOI is assigned phase angle 0/2π, and the phase angle of EOE is generally around π, depending on the shape of the breathing waveform. Assigning phase retrospectively allows us to avoid the issue of phase assignment in real-time, a necessary and very difficult calculation that is needed for clinical gating. Additionally, the analysis should not depend on the choice of algorithm for real-time phase calculation. The retrospective analysis ensures the best possible (if not clinically unachievable) phase assignment.

1. Amplitude-based gating

In this study, the external surrogate’s amplitude-based gating window was chosen to encompass EOI. The gate is opened when the amplitude of the external monitoring system reaches the lower amplitude threshold, and closed when the amplitude falls back below the threshold. A gating window was chosen for each treatment beam such that the duty cycle was approximately 30% with the upper boundary greater than the maximum amplitude of the external surface during that treatment beam. The residual motion is defined to be the motion of internal markers during the open external gating window. For each beam, there is a 3D collection of data points representing the positions of the internal marker when the external amplitude was within the gating window. The median of these points (the median gated position) is the reference point from which the tumor residual motion ($r_{internal}$) is calculated. $r_{internal}$ is the magnitude of the 3D distance between each gated data point and the median gated position. This is the metric of tumor residual motion.
2. Phase-based gating

A similar analysis is performed for the external surrogate’s phase-based gating window. The two phase values that define the boundaries of the gating window are found by an exhaustive search of all phase angle windows in 0.1 rad increments. The gate is selected that results in the lowest residual motion for 30% duty cycle with the requirement of including EOI. This represents the best possible phase gating region for EOI gating. The tumor residual motion is defined to be the collection of internal data points corresponding to the external gating window. The median of these points (the median gated position) is the reference point from which $r_{\text{internal}}$ is calculated, similar to the calculation of tumor residual motion for amplitude-based gating.

III. RESULTS

A. Inhale versus exhale gating

The results of the analysis described above are shown in Table II with the EOE-gated data for comparison. Note that these two analyses (EOI and EOE) were conducted with the same (30%) duty cycle. Also shown is the total internal ungated tumor motion in all three directions (LR, SI, and AP). Even though gating at EOI decreases the tumor motion relative to continuous, ungated treatment, gating at EOE is clearly superior, in this respect. At least some increase in residual motion is seen for every patient when EOI gating is compared to EOE. Averaging the patients, EOI gating gives a mean residual motion of 2.2 and 2.7 mm for amplitude- and phase-based gating, respectively, while EOE gating gives 1.0 and 1.2 mm for the same quantities, respectively. In an alternative analysis of the data, we sought an EOI gate that would produce the same amount of residual motion as the EOE gate, and compared the duty cycles. These results are presented in Table III. For some patients, the EOE residual motion can never be reached with EOI gating. From both of these analyses, we can see that, in the absence of any form of breath coaching, EOE gating is preferable to EOI gating. But how much of this advantage is due to external amplitude reproducibility and how much is due to actual internal/external correlation? In other words, if the external EOI position were reproducible for each breathing cycle, would the residual motion for EOI and EOE gating be equivalent?

We investigated this hypothesis by looking at the relationship between the mean residual motion and the normalized standard deviation of the external maxima, $\langle \sigma \rangle_{\text{inhale}}$, where

$$\langle \sigma \rangle_{\text{inhale}} = \frac{\sigma_{\text{inhale}}}{(1/N)\sum_{i} a_i},$$

$\sigma_{\text{inhale}}$ is the standard deviation of the external maxima (end-of-inhale), $a_i$ is the peak-to-peak external amplitude of the $i$th breathing cycle, and $N$ is the total number of breathing cycles. The normalized standard deviation of the external minima, $\langle \sigma \rangle_{\text{exhale}}$, is similarly defined:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Amplitude-based</th>
<th>Phase-based</th>
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<tbody>
<tr>
<td>1</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>4</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>5</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
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<td>22%</td>
</tr>
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<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>8</td>
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<td>7%</td>
</tr>
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</table>
Figure 3 shows that for amplitude- and phase-based gating, patients with more reproducible EOIs tend to exhibit less residual motion of their lung tumors. Figures 4(a) and 4(b) show the \( \langle \sigma \rangle_{\text{exhale}} \) and \( \langle \sigma \rangle_{\text{inhale}} \) for amplitude- and phase-based gating for patient 6, with each data point representing a single beam. When a patient’s breathing is more reproducible, the residual motion at EOI decreases. This trend is true for all of the patients studied for both gating modalities. Fig. 4(c) is a combination of Figs. 4(a) and 4(b). As the reproducibility of the EOI position becomes similar to that for EOE, the residual motion converges. This means that the residual motion in EOI gating can approach that of EOE gating if the reproducibility of the external position is the same.

A proven method for improving the repeatability of the external signal is patient breath coaching.\(^{16-18}\) Neicu et al. used audio/visual coaching in the form of a “breathe in”/“breathe out” prompt and LCD goggles, showing the patients’ breathing curve in near real-time. The authors of that study have shown that \( \langle \sigma \rangle_{\text{inhale}} \) can be reduced from about 0.22 to 0.11 for free-breathing and audio-visual coaching, respectively.\(^{18}\) In addition, \( \langle \sigma \rangle_{\text{exhale}} \) can be reduced from 0.10 to 0.07, for free-breathing and audio-visual coaching, respectively. These are the averages among ten patients in a clinical setting. The reproducibility of the breath coached EOI position approaches that of the free-breathing EOE position and, in half of the cases studied by Neicu et al., is superior. Extending this result to our patients, we find that if \( \langle \sigma \rangle_{\text{inhale}} \) approaches \( \langle \sigma \rangle_{\text{exhale}} \), the residual motion of the lung tumors will be similar [as seen in Fig. 4(c)].

**B. Phase versus amplitude gating at EOI**

Half of the patients (1, 2, 6, and 8) show less mean residual motion with amplitude-based gating than with phase-based gating, at EOI. The other half shows an insignificant difference (<10%) between the two. The 95th percentile data show that two of the patients (2 and 3) have more significant tails for amplitude gating than phase gating. Otherwise, the data are consistent with the mean residual motion. Overall, the data indicate that an advantageous decrease in residual motion can be achieved by using amplitude-based gating rather than phase-based gating.

We studied the relationship between \( \langle \sigma \rangle_{\text{inhale}} \) and the phase/amplitude-gating question. It was found that reducing \( \langle \sigma \rangle_{\text{inhale}} \) tends to reduce the importance of which gating mode
is selected. This is illustrated in Fig. 5. We define the relative percent difference between the mean residual motions due to amplitude- and phase-based gating to be

\[ \Delta_{\text{phase}} = \frac{\bar{R}_{\text{phase}} - \bar{R}_{\text{amplitude}}}{\bar{R}_{\text{phase}}} \times 100, \]

where \( \bar{R}_{\text{phase}} \) and \( \bar{R}_{\text{amplitude}} \) are the mean residual motions due to phase- and amplitude-based gating, respectively. Among the multi-fraction patients, patient 6 has the largest \( \Delta_{\text{phase}} = 26\% \). The results of Neicu et al. indicate that, with breath coaching, the mean \( \langle \sigma \rangle_{\text{inhale}} \) could drop from 0.28 to 0.17. This new mean \( \langle \sigma \rangle_{\text{inhale}} \) implies a mean \( \Delta_{\text{phase}} \) of 11\%, indicating that amplitude is still better than phase, but by a much smaller margin.

C. Variation in residual motion

We studied the variability of the residual motion, beam-to-beam and day-to-day, throughout the course of treatment. For this part of the study, the first three patients were not analyzed. The mean residual motion as a function of beam and as a function of day, for patients 5 and 6 are shown in Fig. 6. Results are shown for amplitude- and phase-based gating at EOE and EOI. Patient 5 exhibited considerable variation in all modalities at the beginning of treatment, but settled down when he returned for his second course of treatment (days 5–12). Also, the residual motion showed an overall decline throughout the treatment. Patient 6 began with low, consistent residual motion on day 1. It became worse with extreme variation and high residual motion peaking on day 3 before returning to a more constant situation. Overall, EOE gating has systematically less residual motion than EOI for every patient throughout the treatment, in the absence of breath coaching.

Table IV shows the normalized standard deviation of mean residual motion from beam-to-beam for patients 4–8. Here, normalized standard deviation of mean residual motion is

\[ \sigma_{\text{beam}} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (r_i - \bar{r}_i)^2}, \]

where \( r_i \) is the mean \( r_{\text{internal}} \) for beam \( i \) and \( N \) is the total number of beams. With the exception of patient 6, \( \sigma_{\text{beam}} \) is less for EOI gating than EOE. For all patients, \( \sigma_{\text{beam}} \) for amplitude-based gating is less than or approximately equal to phase-based gating. The least amount of beam-to-beam variation can therefore be found in amplitude gating and EOI (except for patient 6, who shows the least amount of variation for amplitude gating at EOE). Table V, shows the same analysis on a day-to-day basis. Similar results are found, with the least daily variation for amplitude gating at EOI (with the exception of patient 6). At this time, we can offer

### Table IV. The normalized standard deviation of beam-to-beam mean residual motion for amplitude- and phase-based gating at EOI and EOE.

<table>
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<th>Exhale</th>
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<tbody>
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<tr>
<td>8</td>
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### Table V. The normalized standard deviation of daily mean residual motion for amplitude- and phase-based gating at EOI and EOE.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Inhale</th>
<th>Exhale</th>
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<tbody>
<tr>
<td></td>
<td>Amplitude</td>
<td>Phase</td>
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<td>0.07</td>
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no explanation for why patient 6 behaves differently. Overall, the change in residual motion for EOI is on roughly the same scale as EOE. That is to say that there can be great changes on the scale of minutes, hours, and days. This varies by patient, but it is unclear how one would predict which patients will have the most/least variability throughout treatment.

IV. DISCUSSION

The residual motion of lung tumors has been studied in eight patients for a hypothetical, externally defined EOI gated treatment. It was found that amplitude-based gating is superior to phase-based gating, but that the difference can be diminished under breath coaching conditions. However, these results were found with the phase computed in an ideal manner (retrospective phase definition and optimized gating window). In general, the phase gating will be worse than this, so amplitude gating may be preferable in a clinical setting. This will be investigated further in future studies. The results were also compared to a previous study, with the same patients, of EOE gated treatment. Upon first inspection, it was found that the latter method produced much less residual motion within the gating window than the former (EOI). However, taking EOI position reproducibility into account, we deduce that the residual motion of breath coached EOI gating will be equivalent to the residual motion of EOE gating. Our deduction is based on the combination of two different experiments. To definitively prove the point, the experiment in Sapporo should be repeated with breath coaching conditions. As such, this data can be studied further with this data.

In our previous study of EOE gating, we expressed our opinion that when gating is based on an external surrogate, some method of verification should be employed during the treatment, to ensure that the tumor is being targeted correctly. We repeat that caveat here. The reduction in EOI residual motion to levels similar to EOE is a good first step towards EOI gating, but to confidently gate at any breathing phase, accurate tumor localization needs to be employed throughout the treatment. This is a problem that we are currently studying.

V. CONCLUSIONS

Respiratory gating at EOI is a clinical option that may be preferable for some patients. The feasibility of producing acceptable tumor residual motion with breath coaching has been shown in this study. Problems due to irreproducibility of the inhale position can be alleviated by the introduction of a biofeedback breath-coaching procedure. We have shown that a reproducible external motion is well correlated with a reproducible internal one. We deduce that under breath-coaching conditions, gating at EOI should produce similar residual motion as EOE, for the same duty cycle.

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15. T. Neicu et al., “Synchronized moving aperture radiation therapy...


