Quantifying the predictability of diaphragm motion during respiration with a noninvasive external marker

S. S. Vedam  
Department of Biomedical Engineering and Department of Radiation Oncology, Virginia Commonwealth University, Richmond, Virginia

V. R. Kini and P. J. Keall  
Department of Radiation Oncology, Virginia Commonwealth University, Richmond, Virginia

V. Ramakrishnan  
Department of Biostatistics, Virginia Commonwealth University, Richmond, Virginia

H. Mostafavi  
Ginzton Technology Center, Varian Medical Systems Inc., Palo Alto, California

R. Mohan  
Department of Radiation Oncology, Virginia Commonwealth University, Richmond, Virginia and Department of Radiation Physics, M.D. Anderson Cancer Center, Houston, Texas

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The aim of this work was to quantify the ability to predict intrafraction diaphragm motion from an external respiration signal during a course of radiotherapy. The data obtained included diaphragm motion traces from 63 fluoroscopic lung procedures for 5 patients, acquired simultaneously with respiratory motion signals (an infrared camera-based system was used to track abdominal wall motion). During these sessions, the patients were asked to breathe either (i) without instruction, (ii) with audio prompting, or (iii) using visual feedback. A statistical general linear model was formulated to describe the relationship between the respiration signal and diaphragm motion over all sessions and for all breathing training types. The model parameters derived from the first session for each patient were then used to predict the diaphragm motion for subsequent sessions based on the respiration signal. Quantification of the difference between the predicted and actual motion during each session determined our ability to predict diaphragm motion during a course of radiotherapy. This measure of diaphragm motion was also used to estimate clinical target volume (CTV) to planning target volume (PTV) margins for conventional, gated, and proposed four-dimensional (4D) radiotherapy. Results from statistical analysis indicated a strong linear relationship between the respiration signal and diaphragm motion ($p<0.001$) over all sessions, irrespective of session number ($p=0.98$) and breathing training type ($p=0.19$). Using model parameters obtained from the first session, diaphragm motion was predicted in subsequent sessions to within 0.1 cm ($1\sigma$) for gated and 4D radiotherapy. Assuming a 0.4 cm setup error, superior–inferior CTV–PTV margins of 1.1 cm for conventional radiotherapy could be reduced to 0.8 cm for gated and 4D radiotherapy. The diaphragm motion is strongly correlated with the respiration signal obtained from the abdominal wall. This correlation can be used to predict diaphragm motion, based on the respiration signal, to within 0.1 cm ($1\sigma$) over a course of radiotherapy.  © 2003 American Association of Physicists in Medicine. [DOI: 10.1118/1.1558675]

I. INTRODUCTION

Reproducibility of target position during and between subsequent fractions of a radiotherapy treatment procedure plays a critical role in increasing the accuracy of the treatment-planning process. The different components that affect such reproducibility of target position include the beam-bony anatomy alignment, displacement of internal organs between fractions, and internal organ motion within a fraction. Depending on the site being treated, each of the above-mentioned components contributes, in varying proportions, to the margins that are to be added around the clinical target volume (CTV),\textsuperscript{1,2} creating the planning target volume (PTV) to ensure adequate coverage throughout the entire course of the treatment. One of the principal causes of intrafraction internal anatomy motion is respiration. Treatment sites that are most significantly affected by such motion include the lung, breast, and liver. Several studies, conducted to examine the extent of diaphragm excursion due to normal respiration, report the range of motion to be between 0.4 and 3.8 cm\textsuperscript{3–7} in the superior–inferior (SI) direction.

During conventional treatment planning to sites affected by respiratory motion, a significant margin is added around the CTV in order to ensure complete coverage of the CTV as it moves due to respiration within a treatment fraction. It therefore follows that a large amount of surrounding normal tissue is irradiated, thus increasing the amount of healthy
lung irradiated and limiting the maximum dose that can be prescribed to the tumor itself. Accounting for such motion during treatment, therefore, has the potential to reduce margins drawn around the CTV, resulting in a lower dose to normal tissues (e.g., lung) and thus a lower risk of treatment-induced complications.8–14

Among the techniques that explicitly account for interfraction motion are breath-hold,6,7,15–20 respiration-gating,21–36 and 4D37 or tumor-tracking38–40 techniques. Breath-hold techniques either actively or passively suspend the patient’s respiration and allow treatment during this interval. A study41 examining intra-and interfraction reproducibility of diaphragm motion during breath holds has indicated that, while diaphragm position within a fraction can be reproduced satisfactorily, daily imaging and repositioning are still required in order to achieve any appreciable reduction in treatment margins. Respiration-gating methods periodically turn the beam on when the patient’s respiration signal is in a certain part of the breathing cycle (generally end-inhale or end-exhale). 4D methods propose to track the tumor with the radiation beam as the tumor moves during the respiration cycle. These techniques require acquisition of some form of respiration signal (infrared reflective markers, spirometry, strain gauges, video tracking of chest outlines and fluoroscopic tracking of implanted markers are some of the techniques employed to date), which is assumed to be correlated with internal anatomy motion. It is obvious that fluoroscopic tracking of implanted markers is well correlated with internal anatomy motion. However, due to the complexity of respiration, it is not so obvious whether the respiration signal from an external marker is correlated with internal anatomy motion.

Mageras et al.,42 in a six-patient fluoroscopic study, presented evidence of a strong correlation between diaphragm motion and the respiration signal. It was also shown that verbal instructions improved the regularity of the respiration signal. Recently, an attempt43 was also made to analyze motion of the actual tumor in the frequency domain from multiple fluoroscopic videos. In Mageras’s study, skin markers served as the respiration signal. Results obtained were on similar lines with a tumor motion range of 0 to 5 cm and an average breathing cycle of 2.8 s. A maximum time delay of nearly a third of a breathing cycle was also observed. In a further study,44 respiratory movement during gated radiation therapy was evaluated by employing film and electronic portal imaging. Among the several parameters examined in this study were intra- and interfraction variability in diaphragm position due to respiration motion. Ozhasoglu et al.,38 in a 5 patient study, examined breathing patterns by employing simultaneous fluoroscopic visualization of internal fiducial markers and external respiration signal recordings (spirometry and optical markers) in real time. They reported significant variations in the breathing patterns, including transient temporal shifts between breathing traces generated by the external marker motion and the motion of the internal anatomy (tumor).

The current literature dealing with respiration-induced organ motion has not statistically evaluated the relationship between the diaphragm motion and the respiration signal for multiple patients, breathing regimens and sessions simulating a course of radiotherapy.

Thus, the main aims of our research were to:

1. Examine the nature of the relationship between diaphragm motion and the respiration signal from multiple repeat fluoroscopic sessions for different patients and breathing training regimens.
2. Use the relationship determined from one “simulation” session to predict diaphragm motion in subsequent “treatment” sessions.
3. Quantify and compare the potential SI margins that need to be added to the CTV for conventional, gated, and 4D radiotherapy.

II. METHODS AND MATERIALS

A. Data acquisition

Sixty-three fluoroscopy movies, typically 30 s each, were recorded from 5 lung cancer patients who participated in a study protocol. Each patient underwent at least two and up to five complete sessions (on different days, with not more than a week separating subsequent sessions) of breathing monitoring (with and without training). Each breathing monitoring session consisted of simultaneous recording of the respiration signal and the fluoroscopy movie, while the patient was asked to breathe (1) normally (no instructions), (2) according to audio prompting (periodic “Breathe in” and “Breathe out” instructions) presented at a rate comfortable for each patient, and (3) by observing a visual representation of the motion trace on a screen and regulating the excursion of the trace between two prespecified motion limits (visual feedback).

The patients were set up in the simulator room by aligning the room lasers with the skin marks as per their treatment chart. The Varian (Varian Medical Systems, Palo Alto, CA 94304-1129) Real Time Position Management (RPM) system was used to acquire (at 30 Hz) the respiration signal, \( R(t) \), and also to simultaneously record a stream of lung fluoroscopy images (at 10 Hz). During each breathing session, the infrared reflective marker was placed at the same point on the patient’s surface, where the magnitude of respiration motion was observed to be high, generally midway between the patient’s xyphoid process and umbilicus. Permanent marker was used to aid in the repositioning of the marker from day to day. A typical patient setup for a study session is shown in Fig. 1.

The respiration signal is the anterior–posterior (AP) component of the infrared reflective marker motion, as measured by the RPM system. Custom-written image-analysis software was developed to allow a user to identify the portion of the diaphragm to be monitored on the first frame of the fluoroscopy movie. The software then automatically updates the SI position of the selected portion of the diaphragm on subsequent frames, thus yielding a motion trace of the diaphragm, \( F_{\text{act}}(t) \).31 For each fluoroscopy session, the apex and the lateral and medial aspects of the diaphragm were tracked when
B. Relationship of respiration signal to internal anatomy motion: Statistical validation of a general linear model

The first step was to statistically validate the assumption that the relationship between the respiration signal and internal anatomy motion could be expressed satisfactorily with the mathematical model of the form expressed in Eq. (1). A linear model relating the two variables \( F_{\text{act}}(t) - F_{\text{act}} \) and \( R(t - \delta) - R \) was statistically fitted. Since this correlation may be influenced by the variability in breathing training types and sessions, these variables were included in the linear regression model to obtain an adjusted estimate of the correlation between the two variables. As the same subjects were repeated over the sessions and training types, these variables were included in the linear model. Thus, from the respiration trace of subsequent sessions we can predict the diaphragm motion using

\[
F_{\text{pred}}(t) = F_{\text{act}} - c_0 \times (R(t - \delta) - R),
\]

where \( c_0 \) and \( \delta_0 \) are the average ratio and time delay values established from the initial (simulation) session.

The validity of the predicted trace, \( F_{\text{pred}}(t) \), to represent the actual trace, \( F_{\text{act}}(t) \), can be quantified by taking the standard deviation of the relative positional differences between these traces, \( \sigma_{F_{\text{pred}} - F_{\text{act}}} \) for a given session. Obviously, the smaller the value of \( \sigma_{F_{\text{pred}} - F_{\text{act}}} \), the better the internal motion can be predicted from the respiration signal. This internal motion prediction can be used in 4D radiotherapy to track the tumor based on the respiration signal.

Also of relevance for gated radiotherapy is the quantification of the internal motion prediction during the gating window when the beam is on. This quantity, which is denoted as \( \sigma_{F_{\text{Gate}}F_{\text{act}}} \), indicates the variation between the predicted tumor motion and actual tumor motion within a specified gating window. For gated radiotherapy, respiration-induced motion occurs during the finite window. As the duty cycle increases, the residual motion within the gating window, defined as \( \sigma_{F_{\text{act}}} \), also increases. [The duty cycle, or efficiency, as defined here is the ratio of beam on time (when the respiration signal falls within the gating window) to total beam delivery time. Delivering 150 monitor units at 300 monitor units per second without gating would normally take 30 s. With a 25% duty cycle, this will take 2 min.] For this study, the gating windows were chosen at 20%, 35%, and 50% duty cycles for both inhale and exhale to cover the range of clinically used values.
D. Calculation of superior–inferior CTV to PTV margins

Because intrafraction motion is one component of the margin that needs to be added to the CTV to obtain the PTV, gating and 4D methods that explicitly account for tumor motion during delivery will have a small CTV–PTV margin. However, because improved technology and setup error inaccuracy did not differ significantly over the different breathing training types (normal breathing, audio prompting, visual feedback), the following equations for conventional ($M_{\text{Conv}}$), gated ($M_{\text{Gate}}$), and 4D ($M_{4D}$) margins were derived:

\[
M_{\text{Conv}} = 2 \times \sqrt{\sigma_{\text{setup}}^2 + \sigma_{F,\text{act}}^2},
\]
\[
M_{\text{Gate}} = 2 \times \sqrt{\sigma_{\text{setup}}^2 + (\sigma_{F,\text{gate}} - \sigma_{F,\text{act}})^2},
\]
\[
M_{4D} = 2 \times \sqrt{\sigma_{\text{setup}}^2 + (\sigma_{F,\text{gate}} - \sigma_{F,\text{act}})^2},
\]

where $\sigma_{\text{setup}}$ includes both the variation in patient position (beam-bony anatomy alignment) and the bony anatomy–tumor alignment (bony anatomy–diaphragm in this case). $\sigma_{F,\text{act}}$ represents the variation of the actual diaphragm motion throughout the entire breathing session.

For this study, the setup error used was the realistic value of 0.4 cm. However, because improved technology and techniques may reduce setup errors in the future, setup error values of 0.2 cm were also used for the margin calculations.

III. RESULTS

A. Quantification of diaphragm motion

For the purposes of margin calculation, the complex nature of the diaphragm motion [see, for example, Fig. 4(a)] can be quantified by calculating the standard deviation of the motion (assuming that the probability distribution of the position with time is approximately normally distributed). Table I provides values of the diaphragm motion ($\sigma_{\text{act}}$) for each patient and for the different types of breathing training, averaged over multiple fluoroscopy sessions. Diaphragm motion during visual feedback was comparable to that obtained during normal breathing. However, audio prompting increased the range of amplitude of diaphragm motion. This result was found to be consistent with the observations made in a previous study.

Diaphragm motion within different gate intervals (20%, 35%, and 50% duty cycle at inhale and exhale) for the free-breathing data is shown in Fig. 2. In general, motion within gate intervals at exhale was less than that at corresponding gate intervals at inhale. An increase in the width of the duty cycle, or gating window resulted in an increase in motion extent, as shown in a previous study. Note that the motion with a 100% gate interval is the same as that obtained over the entire breathing session.

B. Relationship of respiration signal to internal anatomy motion: Statistical analysis using the repeated measures mixed effects model

A repeated measures mixed effects model was fitted using the PROC MIXED procedure in SAS (SAS Institute Inc., Version 8.2e, 2000, Cary NC) to statistically evaluate Eq. (1). A scatter plot of the diaphragm motion, $F_{\text{act}}$, and the respiration signal, $R$, for every measurement point obtained ($\sim 10000$) is shown in Fig. 3. An analysis of the data shows that even though the multiple recording sessions and breathing instruction types changed the respiration patterns, the relationship between respiration signal and diaphragm motion did not differ significantly over the different breathing types ($p = 0.19$) or session number ($p = 0.98$), as shown in Table II. However, the diaphragm motion is strongly correlated with the respiration signal ($p < 0.0001$), and the use of a linear model is justified. In addition, results obtained ($p < 0.0001$) when Time (instant of time during the breathing cycle) is considered as a factor and those obtained for the interaction variables—Time, Respiration signal×Time,
Respiration signal \times Session number, and Respiration signal \times Breathing training type—do suggest the existence of a significant variation in the slope of the line of fit with respect to time instant during the breathing cycle, session number, and breathing training type.

To interpret the statistical results in a more visual manner, the diaphragm motion and respiration signal traces, representing the session with the lowest diaphragm motion—respiration signal correlation (an outlier) and the highest correlation, are shown in Fig. 4. This figure shows that even for the lowest observed correlation (0.51), similarities still exist between the diaphragm motion and respiration signal. Note that the mean correlation observed for individual sessions was 0.94.

Table II. Estimation of coefficients for the general linear model ($p$ values), expressing the relationship between respiration signal and diaphragm motion. The session number was the session for each patient corresponding to the different days on which subsequent fluoroscopy studies were performed. The breathing training type is either normal breathing, audio prompting, or visual feedback.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration signal</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Session number</td>
<td>0.98</td>
</tr>
<tr>
<td>Breathing training type</td>
<td>0.19</td>
</tr>
<tr>
<td>Time</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Respiration signal $\times$ Time</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Respiration signal $\times$ Session number</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Respiration signal $\times$ Breathing training type</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\[FIG. 3.\] Scatter plots representing (a) the overall relationship between diaphragm position, $F_{\text{act}}$, and respiration signal, $R$, for all data points (~10 000) from all (63) of the fluoroscopic sessions and (b) patient-specific relationships between diaphragm position, $F_{\text{act}}$, and respiration signal, $R$. The line of best fit in each case and the correlation values are also displayed. Note that positive values on both axes correspond with the inhale phase of the breathing cycle.
C. Prediction of diaphragm motion

The ability of the respiration signal to predict the diaphragm motion based on Eq. (1) is summarized in Table III. These results were obtained by including all sessions of the same training type for all of the patients in the analysis. The results show a consistent ability to predict the diaphragm motion to within ~0.1 cm (1 σ), independent of breathing training.

These results represent our prediction ability over the entire breathing cycle and are applicable to 4D treatments. A similar analysis performed for gated treatments is shown in Fig. 5, again showing the ability to predict the diaphragm motion to within 0.1 cm at different duty cycle values.

D. Calculation of superior–inferior margins for different treatment modalities

The values obtained for predicted diaphragm motion were entered into Eqs. (3)–(5) to determine the CTV–PTV margins that would be needed to have the CTV within the PTV 95% of the time. The results are shown in Fig. 6. All margin reductions from the conventional values shown are significant at the 1% level, except for the results of gated exhale for the 50% duty cycle.

With gated therapy, the degree of margin reduction decreased with an increase in the width of the gate (duty cycle) due to residual motion within the gating window. The potential margin reduction was greater as setup error became less significant. 4D radiotherapy allows the greatest margin reduction, since there is no residual motion within the gating window.

IV. DISCUSSION

Many gated, breath-hold and 4D radiotherapy techniques rely on using a respiration signal as a surrogate for or predictor of tumor motion. Verifying this assumption was an aim of this research. In this study, diaphragm motion and respiration signal (abdominal wall motion) were correlated in over 60 fluoroscopy sessions. Statistical analysis showed that these two quantities are strongly correlated. Ozhasoglu et al.38 also report in their work a similar correlation between the superior–inferior displacement of a pancreas tumor and the anterior–posterior displacement of an external chest marker. They also suggest that if such a stationary relationship can be established, then a correlation between the external chest marker and the tumor motion can be derived from three or four randomly timed observations of both signals and hence be extrapolated into the future. We adopted a similar approach in our study when we first established such a stationary relationship between the external respiration signal and the diaphragm as a surrogate for tumor motion. The correlation derived, based on such a stationary relationship for a “simulation” session, was then used to predict dia-

TABLE III. Measure of ability to predict (1σ) diaphragm motion, σ_{F_{pred}–F_{act}} in multiple sessions (cm).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normal breathing</th>
<th>Audio prompting</th>
<th>Visual feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.08</td>
</tr>
<tr>
<td>2</td>
<td>0.08</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>0.07</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>0.09</td>
<td>0.11</td>
<td>0.07</td>
</tr>
<tr>
<td>5</td>
<td>0.11</td>
<td>0.1</td>
<td>0.14</td>
</tr>
<tr>
<td>All</td>
<td>0.09</td>
<td>0.09</td>
<td>0.11</td>
</tr>
</tbody>
</table>
has been studied by Ford et al.44,45 using fluoroscopy, respiratory gated film, and electronic portal imaging data acquired from eight patients. In their study, the patient averaged interfraction diaphragm range of motion of 0.69 cm during normal respiration. The corresponding results, presented as standard deviations of motion, are 0.36 and 0.11 cm, respectively, and are therefore consistent with the range of motion values reported by Ford et al.44

A limitation of the current work is that only the motion of one anatomical structure (the diaphragm) and only one respiratory signal (abdominal wall motion at the midway point between the umbilicus and xyphoid process) has been correlated. However, breathing patterns show a lot of variations over the course of time. Hence, longer treatment times directly influence the stationary nature of the correlation between the respiratory signal and tumor/diaphragm motion. Also, the presence of a phase shift 31,38,42,45 transient or otherwise between the external and internal motion signals, as reported in the literature, has to be accounted for. In the current study, we observe a phase shift. Such a shift, if and when it occurs, will affect the results obtained from this study. Of most importance, therefore, is correlating the tumor motion with the respiratory signal. This correlation may be possible with the development of respiration-correlated “4D” CT methods.47–53

Patient training using audio and visual aids does affect amplitude of breathing patterns, as is evident from results in Sec. III A. Audio instructions tend to increase the amplitude of breathing while visual aids could potentially be used to limit diaphragm excursion to predetermined levels. However, training does not seem to have a significant effect on our ability to predict the diaphragm motion during treatment sessions.

Intrafraction motion, which was the main focus of our work, is just one of several components that contribute to increased margins. The issues of interfraction motion and setup error have already been studied and reported in literature. Balter et al.54,55 have analyzed diaphragm position on daily radiographs from eight patients to assess setup variations in liver position during breath-hold treatments with the ABC device. Analysis of repeat 3D CT scan data obtained from this method indicated a reduction in setup errors (1 σ) from 6.7 to 3.5 mm (superior–inferior), 4 to 2.1 mm (left–right, LR), and 3.8 to 2.3 mm (anterior–posterior, AP) respectively. Dawson et al.,41 using a similar technique, have reported interfraction SI reproducibility (1 σ) of 4.4 mm. In a study of interfraction diaphragm variation during respiratory gated radiotherapy, Ford et al.44 reported patient averaged interfraction diaphragm variability of 2.8±1.0 mm, based on data obtained from gated localization films. The study further concluded that most of the variability in diaphragm position occurs due to setup errors rather than respiratory motion. Thus, while gated and 4D treatments exhibit a potential for margin reduction as compared with conventional treatments, this margin reduction is still limited by the magnitude of the setup error.

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Author to whom all correspondence should be addressed; electronic mail: pkjeal@vcu.edu


