

# Deep Inspiration Breath Hold and Respiratory Gating Strategies for Reducing Organ Motion in Radiation Treatment

Gikas S. Mageras and Ellen Yorke

**We examine 2 strategies for reducing respiration-induced organ motion in radiation treatment: deep inspiration breath hold (DIBH) and respiratory gating. DIBH is a controlled breathing technique in which the patient performs a supervised breath hold during treatment. The technique offers 2 benefits: reduced respiratory motion from the breath hold and increased normal tissue sparing from the increased lung volume. In respiratory-gated treatment, a device external to the patient monitors breathing and allows delivery of radiation**

**only during certain time intervals, synchronous with the patient's respiratory cycle. Gated treatment offers reduced respiratory motion with less patient effort than DIBH. We briefly survey the development of these 2 strategies, describe their clinical implementation for treatment of thoracic and liver tumors at the Memorial Sloan-Kettering Cancer Center, and discuss their advantages and limitations.**

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**I**nterventional strategies for managing respiration in radiation treatments have received increased attention in recent years. These developments have been motivated by the advances in high-precision radiotherapy, together with recognition of the importance that physiologic processes, among them respiration, have in limiting the accuracy of dose delivery. In addition, advances in technology have spawned new types of detectors for measuring and reducing respiratory-induced motion. This article examines 2 such strategies: the use of controlled patient breathing, specifically, deep inspiration breath hold, and respiratory gating of the linear accelerator while the patient breathes normally. The potential dosimetric benefits, implementation, and clinical experience with these techniques are discussed.

## Deep Inspiration Breath Hold Technique

A reproducible state of maximum breath hold (deep inspiration breath hold [DIBH]) is advantageous for treatment of thoracic tumors because

it significantly reduces respiratory tumor motion and changes internal anatomy in a way which often protects critical normal tissues. Several methods for implementing DIBH are described later. All require patient compliance and active participation and often extra therapist participation.

### DIBH Methods

A spirometer-monitored method (see the section on clinical implementation of DIBH) was developed, evaluated, and clinically implemented, mainly for non-small-cell lung cancer (NSCLC) at Memorial Sloan-Kettering Cancer Center (MSKCC).<sup>1-3</sup> Other methods have been implemented elsewhere. Kim et al<sup>4</sup> reported a 16-patient feasibility study of "self-gated radiotherapy" in which patients control an interlock of a modified linear accelerator; the therapist turns on the beam when the patient judges that he has attained the correct breath hold level. A subsequent study by Barnes et al<sup>5</sup> found that 8 out of 10 patients could comply with this process. Onishi et al<sup>6</sup> have also reported on a self-initiated breath hold technique without a respiratory device. Wong et al<sup>7</sup> showed the reproducibility of active breathing control (ABC) at various phases of the breathing cycle for patients with thoracic cancer. Imaging studies of ABC-assisted DIBH have been done for Hodgkin's disease and breast cancer patients.<sup>8,9</sup> ABC-assisted breath hold at 75% maximum capacity (modified DIBH [mDIBH]) has also been reported<sup>10</sup> and used for treatments of breast and other thoracic cancers (John Wong, personal communication).<sup>11</sup> The ar-

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ticle by James Balter and Laura Dawson in this issue further discusses ABC and other controlled breathing techniques.

### **Benefits of DIBH for Treatment of Thoracic Tumors**

**Reduction of respiratory motion.** In a feasibility study of the MSKCC spirometer-monitored method, Hanley et al<sup>1</sup> analyzed fluoroscopic movies of 5 patients and found average intrabreath hold deviation of the lung-diaphragm boundary position of 0.1 cm and interbreath hold reproducibility of 0.25 cm (range 0.05-0.49 cm); with normal breathing the average motion was 2.64 cm. The lung-chest wall boundary was similarly reproducible. On duplicate DIBH CT slices, they measured an average 3% lung area change for images acquired under deep inspiration versus 11% change between images acquired at shallow inspiration and shallow expiration.<sup>1</sup> Consistent results were reported by Mah et al<sup>3</sup> in an analysis of fluoroscopic movies of the first 7 patients treated with this technique. Furthermore, on 92 anterior-posterior (AP) port films, they found that the average diaphragm-to-isocenter distance differed from the simulation digitally reconstructed radiograph by  $-0.1 \pm 0.4$  cm (mean  $\pm$  1 SD; range  $-1.2$  to  $1.1$  cm), indicating good overall diaphragm reproducibility over the course of treatment. Using diaphragm as a surrogate for tumor motion, Hanley et al<sup>1</sup> suggested that, with DIBH, the expansion margin from gross tumor volume (GTV) to planning target volume (PTV) can be reduced, so less normal tissue need be irradiated.

Other DIBH studies have reported similar results. Kim et al<sup>4</sup> found the self-gating method to yield intrasession diaphragm variation from 0.01 cm to 0.76 cm and intersession variation (4 patients/3 sessions each) of less than 0.05 cm. In ABC-assisted imaging studies, Wong et al<sup>7</sup> found an average intrabreath hold diaphragm excursion of  $0.15 \pm 0.18$  cm and intersession (1 week apart) variation of  $0.4 \pm 0.33$  cm. Stromberg et al<sup>8</sup> reported intersession lung volume variation (DIBH scans on 2 different days) of  $4\% \pm 4\%$ .

**Normal tissue protection.** For the first 7 patients treated with DIBH at MSKCC (all NSCLC patients), Rosenzweig et al<sup>2</sup> found the average lung volume increased by a factor of 1.9 relative to normal breathing, thus reducing the fraction of normal lung tissue irradiated. Because dosi-

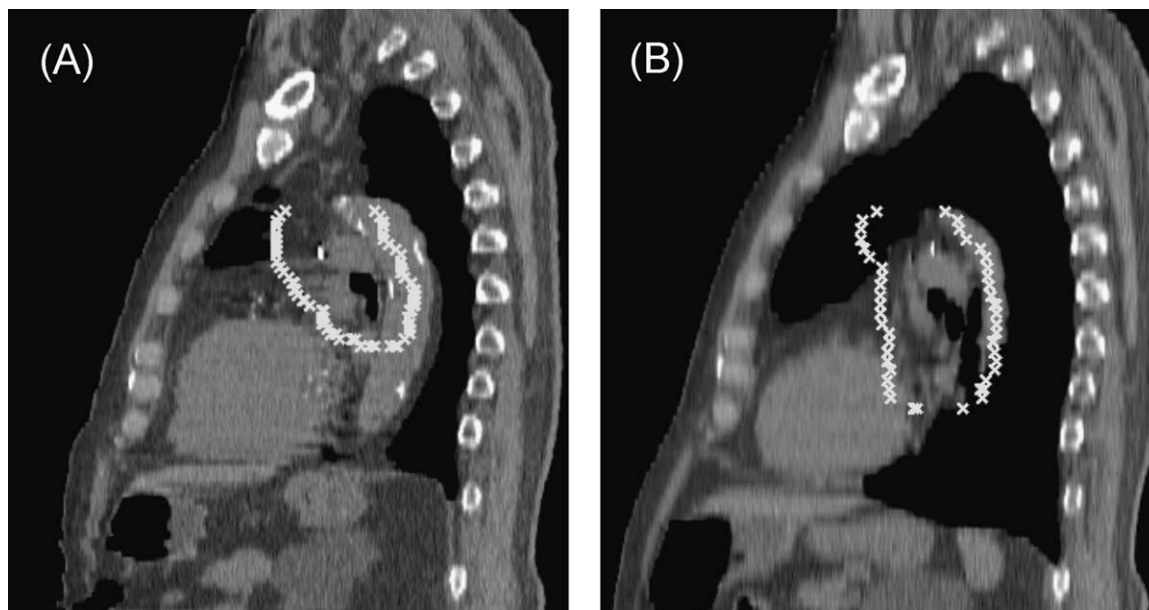
metric predictors of radiation pneumonitis depend strongly on the fraction of irradiated lung, DIBH permits higher total treatment doses for the same predicted lung toxicity. Comparing 3-dimensional (3D) conformal radiation treatment plans for standard normal breathing (NB) and DIBH CT scans of these patients, restricting the Lyman model lung normal tissue complication probability to no more than 25% and maintaining the same GTV-to-PTV margin, they found DIBH increased the average prescription dose from 69.4 Gy with NB to 87.9 Gy with DIBH. For some patients, DIBH also displaces the GTV away from the spinal cord (Fig 1).<sup>12</sup>

Likewise, for NSCLC treatment plans and a prescription dose of 70.9 Gy to isocenter, Barnes et al<sup>5</sup> found that, on average, self-gated DIBH decreased the percent of lung volume receiving  $>20$  Gy (V20) from 12.8% (NB) to 11% (DIBH) without and to 8.8% with GTV-to-PTV margin reduction. For Hodgkins disease, ABC-assisted DIBH significantly reduced lung and heart irradiation relative to NB.<sup>8</sup>

Advantages were shown for treatment of breast cancer with DIBH or mDIBH. In a feasibility study, Sixel et al<sup>9</sup> found that ABC-assisted DIBH was well tolerated and reduced V<sub>25</sub> in 3 of 5 conventional tangent plans and 4 of 5 cases wide tangent plans. In another planning study, Sidhu et al<sup>13</sup> found lower mean heart and liver dose for, respectively, left- and right-sided breast tangents with DIBH. Remouchamps et al<sup>10</sup> compared NB and ABC-assisted mDIBH for treatment plans of breast plus internal mammary nodes. For wide tangents matched with electron fields they reported that mDIBH "significantly reduces heart and lung doses." A subsequent report describes treatment of 15 patients (13 breast cancer, 2 lung cancer) with ABC-assisted mDIBH.<sup>11</sup>

### **Clinical Implementation of DIBH at MSKCC**

DIBH has been used to treat 37 patients at MSKCC (36 with NSCLC) since February 1998.<sup>2,3</sup> The patient, with nose clamped, breathes through a calibrated pneumotach spirometer and is coached through a modified slow vital capacity (SVC) maneuver, consisting of tidal breathing, a maximum inspiration, maximum expiration, and a second maximum inspiration with breath hold. In-house software displays the spirometer output

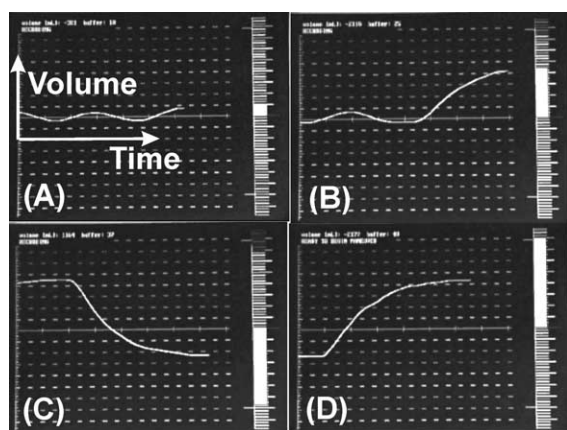


**Figure 1.** Sagittal section of (A) free breathing CT and (B) DIBH CT. For some patients, the use of DIBH moves the tumor (outline) away from the cord.

on a laptop computer (Fig 2).<sup>1,3</sup> Volumes at key points in the trace are compared with user-set values and changes in the color of the bar graph at the right of the display help the coach verify reproducible performance of the SVC maneuver, as shown and described in Figure 2. To prevent CO<sub>2</sub> buildup, the spirometer is reinitialized after

each breath hold. Because most patients can maintain DIBH for 15 to 20 seconds, up to 220 monitor units (MU) can be delivered in a single breath hold at the maximum linear accelerator dose rate (500 or 600 MU/min).

**Simulation.** Because approximately half of our patients cannot comply with aspects of DIBH, potential patients are first screened. Simulation, which takes approximately 2 hours, includes immobilization, isocenter selection, a DIBH practice session (which also provides initial threshold values) and 3 helical CT scans in the treatment position, one NB scan, and 2 spirometer-monitored scans (one each at DIBH and at shallow inspiration [SI]). The DIBH and SI scans are split into breath hold segments of 10 to 12 seconds each. The NB scan (<1 minute) confirms reproducible vertebral positioning for DIBH and NB so that NB treatment setups can be done with the patient breathing normally. Also, if the patient cannot be completely treated with DIBH, the NB scan is used for treatment planning, whereas for DIBH treatments, the DIBH scan is used. The SI scan provides information about GTV position changes for a known change in respiration to set breath hold tolerance levels.<sup>3</sup> Consistency during the DIBH CT scan is necessary for proceeding to DIBH treatment; inconsistent exhale and/or



**Figure 2.** Computer display of the spirometer trace (air volume vs time) of a patient performing a DIBH hold maneuver: (A) tidal breathing, (B) first deep inspiration, (C) deep expiration, and (D) second deep inspiration and breath hold. The bar graph at the right of the display is the time-integrated flow rate since the last change in flow direction.

deep inhale levels imply that normal breathing should be used for planning and treatment.

**Treatment planning.** The DIBH treatment plan usually involves 2 to 6 patient-specific static conformal fields, but sliding window IMRT delivered dynamically with multileaf collimation,<sup>14</sup> having relatively low MU per field, can be used for patients with good breath hold capability. Despite reduced respiratory motion, the GTV-to-PTV margin of 1 to 1.5 cm is not reduced for 3 reasons: (1) deep inspiration (DI) lung expansion of normal lung away from the irradiated region allows sufficient target dose escalation with acceptable estimated lung toxicity,<sup>1,2,15</sup> (2) the margins protect against possible expansion of microscopic disease because of DI, and (3) our treatment planning dose calculation algorithm does not handle lateral disequilibrium in low-density tissue but Monte Carlo studies suggest that the NB margins (GTV-to-aperture edge) adequately cover the GTV if 6 MV photons are used.<sup>15</sup>

**Treatment.** The patient performs the DIBH maneuver for all treatment fields and portal images, all of which are delivered at maximum dose rate. Most treatments are completed in less than 20 minutes. New therapists are trained on the entire procedure. A weekly AP port film showing the entire lung is used to confirm approximate constancy of the lung inflation (distance from the lung apex to dome of the diaphragm). If these films or the graphic spirometer traces indicate that the SVC maneuver is becoming irregular, the physician and physicist evaluate dosimetric consequences and remedies.

Although DIBH allows dose escalation for tumors in or near the lung, it has 2 major disadvantages. The need for active patient participation and compliance severely limits the number of patients who can benefit from it. In addition, the short duration of any tolerable single breath hold makes DIBH incompatible with positron-emission tomography imaging, which typically requires 3 to 10 minutes per bed position.

### Respiratory Gating

In respiratory-gated treatment, a device monitors patient breathing and allows delivery of radiation only during certain time intervals, synchronous with the patient's respiratory cycle. As discussed earlier, controlled breathing such as DIBH requires patient cooperation and additional staff

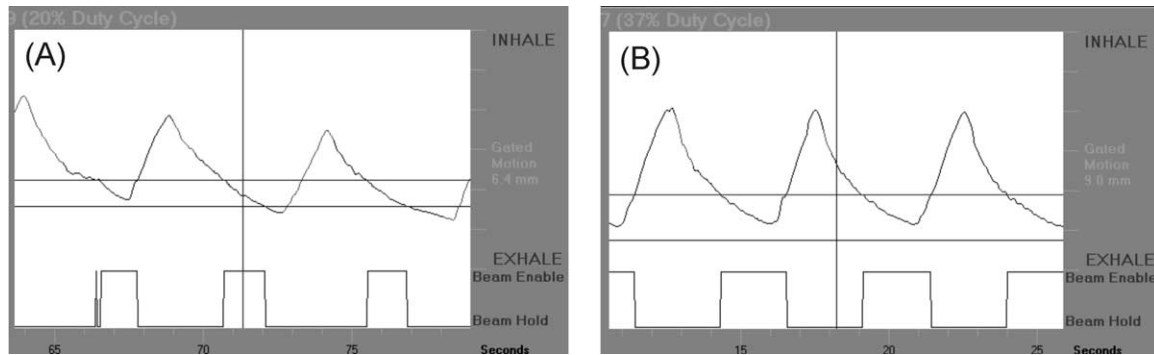
time and effort. Moreover, deep inspiration may not be an advantage in some disease sites subject to respiratory motion, such as liver. In contrast, respiration gating with the patient breathing normally is potentially less demanding and thus more generally applicable. In this article we will focus on gating systems that rely on respiration monitors external to the patient to infer the position of internal target organs. The article by Martin Murphy examines systems that use real-time imaging of patient internal anatomy.

Clinical programs of respiratory gated radiotherapy were introduced over a decade ago in Japan. The Tsukuba Proton Medical Facility reported on a combination airbag and strain gauge taped on the patient's abdomen or back (for prone treatments) to gate a proton beam.<sup>16,17</sup> Other centers have used position sensors placed on the patient to gate a linear accelerator<sup>18</sup> or a heavy ion beam.<sup>19</sup> Hokkaido University has developed a gated linear accelerator system using real-time fluoroscopic tracking of gold markers implanted in tumor,<sup>20</sup> described further in the article by Martin Murphy. The International Medical Center of Japan has investigated stereotactic treatments of lung tumors in a single fraction of 20 to 30 Gy, lasting 1 to 2 hours when gated with a position-sensitive monitor at end expiration.<sup>21</sup>

In the United States, the University of California at Davis reported on the first feasibility study of gated radiotherapy with a Varian 2100C accelerator in 1996.<sup>22</sup> Subsequently, they described a gated radiotherapy system, developed jointly with Varian Medical Systems, which accepts respiratory signals from either a video camera (now commercially available as the real-time position management respiratory gating system [RPM]) or from an inductive plethysmograph that is wrapped around the patient torso.<sup>23</sup> A number of centers have reported on clinical studies with the RPM system, which is described further later.<sup>24-27</sup>

### RPM System Description

The RPM system permits breathing-synchronized CT acquisition and fluoroscopy on a conventional simulator, as well as gated treatment on a linear accelerator. To monitor respiration, a lightweight block containing 2 passive reflective markers is placed on the patient's chest or abdomen. Infrared light from an illuminator is re-



**Figure 3.** (A) A patient breathing waveform from the RPM system, with thresholds (horizontal lines) set for amplitude-based gating at expiration. The tick marks on the horizontal axis are time in seconds, and on the vertical axis, they are distance in centimeters. The square wave graph at the bottom of the display indicates when the treatment beam would be enabled. Toward the right, irregular breathing causes in a drift in the waveform, resulting in beam enable at the wrong point in the breathing cycle. Breathing was recorded without audio prompting. (B) Waveform of the same patient, recorded with audio prompting.

flected from the markers and detected by a charge-coupled-device video camera. The upper marker serves to track respiratory movement, whereas the lower marker, separated from the upper one by 3 cm, serves to calibrate the system. A vendor-supplied program running on a desktop computer processes the video signals and sends on-off control signals to a linear accelerator. At the start of each session, the operator places the system into a so-called tracking mode for a few breathing cycles, to allow the system to determine the minimum and maximum vertical position of the upper marker. In addition, a periodicity filter algorithm checks that the breathing waveform (ie, the marker position  $v$  time) is regular and periodic. Once breathing is stable and regular, the operator places the system into a record mode, during which the breathing waveform is recorded and displayed. There are 2 modes of producing gate signals: amplitude or phase. In the amplitude-based mode, user-adjustable threshold levels are superimposed as 2 horizontal lines on the waveform and are calculated relative to the minimum and maximum marker position measured during the tracking mode (Fig 3A). During treatment, the beam is delivered only when the breathing waveform is between the upper and lower threshold lines. In addition, the periodicity filter immediately disables the beam when the breathing waveform becomes irregular, such as patient movement or coughing, and re-enables the beam after establishing that breathing is again regular. In the phase-based mode,

the operator specifies a phase interval of the breathing waveform calculated by the periodicity filter algorithm. On a conventional simulator, the RPM system allows recording and playback of fluoroscopy images, synchronized with the external breathing motion waveform. Only those fluoroscopy frames occurring within the gate intervals are played back. The operator can examine anatomic motion in the playback to evaluate and optimize the gate.

For planning gated treatment, it is essential to acquire a CT scan at the same part of the respiratory cycle as the treatment. The infrared illuminator camera assembly is mounted at the foot of the CT couch to properly track the respiration signals during the CT scan. Some types of scanners accept signals directly from the RPM system: the CT is operated in axial scan mode and each gate-enable signal triggers the acquisition of an axial slice, followed by a table advance to the next slice position. Because only 1 slice is acquired per respiratory cycle, a CT scan of 100 slices requires 5 to 8 minutes for a breathing period of 3 to 5 seconds. For scanners that cannot accept external triggers, the acquisition of each slice must be triggered manually while watching the respiration waveform on the RPM system.

#### RPM Clinical Implementation at MSKCC

In late 1999, MSKCC initiated clinical studies with the RPM system. As of this writing, 37 patients (22 NSCLC and 15 liver cancer) have received gated static field treatment or IMRT. Res-

piratory-gated treatment for liver cancer patients has enabled a safe reduction of margins (GTV to PTV) from 2 cm to 1 cm, subject to continuing port-film surveillance during treatment.<sup>25</sup> Gated treatment with RPM is well tolerated by most patients and requires less effort than DIBH on the part of technical staff; however, some patient effort and concentration is required, along with considerable care and patient-specific quality assurance on the part of all involved staff. We use simple, repetitive verbal coaching instructions to improve breathing regularity for all gating patients. Before simulation, the instructions are customized to the patient's breathing rhythm (lengths of time between successive phrases, "breathe in," "breathe out," "breathe in") using a feature of the RPM system and played during acquisition of planning images and treatments. We also find that, despite instructions to the patients to inhale normally, the marker waveform with instructed breathing shows larger amplitude compared with uninstructed breathing for almost all patients (Fig 3B). A recently introduced RPM feature is a visual display (small LCD monitor mounted on the couch) to assist the patient in maintaining consistent marker amplitude (and by inference, breathing amplitude). We have used this feature for 7 patients to date and are still evaluating its efficacy. We presently use amplitude gating for all patients because early versions of the RPM software were more robust with amplitude than with phase gating and we have not yet reevaluated phase gating.

**Simulation.** MSKCC has RPM systems installed on a conventional simulator (Ximatron; Varian Medical Systems, Palo Alto, CA) and a CT-Simulator (AcQSim PQ5000; Philips Medical Systems, Bothell, WA). Because there is heavy demand on CT scanner time, preparation of the gating patient is done at the conventional simulator. After an approximately 5-minute system check, a physicist explains the gating procedures to the patient (the physician has already explained the rationale for gating). After patient immobilization, the marker block position is selected and its position is tattooed for reproducible placement. Varian recommends waveform motion extent (peak to peak) of at least 0.5 cm; we find that a midline location approximately two thirds of the way between umbilicus and xyphoid gives sufficient signal. The voice instruction is customized, and the physician picks a starting

isocenter location. We acquire an approximately 45-second voice-instructed fluoroscopic movie and an AP film, which includes the isocenter, ipsilateral diaphragm, any tumor shadow, and spine. The superior visualization of subtle vertebral features on the kV film is helpful for comparison with port films. The gate width and the amplitude of the marker motion (for visual feedback) are tentatively established. Conventional simulation takes 45 to 60 minutes, with physics assistance throughout.

**CT simulation.** Set-up and testing the RPM components at the scanner takes approximately 10 minutes. Because we have not yet implemented visual feedback at the conventional simulator, the physicist trains the patient to follow the combination of audio and visual prompting. In addition to the longer scan time with respiration triggered CT described earlier, irregular breathing further slows the process, requiring restarting the scanner to correct for artifacts near the target or diaphragm. Two complete CT image sets are acquired to allow an estimate of interfraction variability, and the patient is encouraged to rest between scans. The more regular of the 2 image sets is used as the planning scan. Typical time for the CT simulation is 1 to 1.5 hours, with direct physics involvement throughout.

**Treatment.** No special treatment planning measures are taken for gating patients; either static 3D conformal radiotherapy or IMRT is used, at the discretion of the physician and the planner. For NSCLC patients, we have not reduced the PTV margin that has been used for conventional treatment but rather assign patients to gated treatment if there is evidence of tumor mobility. Both audio and visual prompting is used for treatment. New therapists are regularly trained by a designated physicist; the therapists must carefully watch the respiration waveform during treatment, stop treatment to remind the patient or check setup if they see serious irregularity or drift, and contact a designated physicist for persistent problems. Gated treatment is well accepted by patients and therapists. Gated treatment session times are increased relative to standard treatments by 5 to 10 minutes depending on patient compliance. Routinely, for each patient, we acquire AP localization films including the diaphragm and vertebral landmarks (3 films per week for the first 2 weeks of

treatment, twice per week for the next 2 weeks if no systematic differences are observed, and at least once per week thereafter). To keep the imaging dose low yet get a clear image, we use 4 MU. Currently, RPM-synchronized electronic portal imaging ( $\sim 1$  MU/image) is only available on research systems and requires extensive physics support. If systematic errors in excess of 0.4 to 0.5 cm are observed, the physician is consulted as to the need for field adjustment. To date, field adjustments have been made for 5 (out of 37) patients.

### Equipment-Related Quality Assurance

The commissioning of a gated radiotherapy system should include measurements to assure that gating does not significantly change beam characteristics. Such changes are likely to be accelerator dependent and should be checked for each treatment unit. For gated operation of Varian Clinac 2100C and 2100EX accelerators with the RPM system, we have found negligible changes in output, tissue-maximum ratio, flatness, and symmetry when delivering 100 MU at dose rates of both 300 MU/min and 600 MU/min, consistent with the earlier findings by Kubo and Hill<sup>22</sup> and more extensive studies by Ramsey et al.<sup>28</sup> Additional commissioning should be performed for gated IMRT delivered with dynamic multileaf collimation. We have performed ion chamber and film dosimetry on both of the previously mentioned machines and found that gated beam delivery does not significantly change the IMRT dose distributions, even at the highest available dose rate.<sup>29</sup> Kubo and Wang<sup>30</sup> also have reported that RPM-type gating is consistent with sliding window dynamic multileaf collimation. System acceptance includes a test of the consistency of gated operation between conventional simulator, CT, and linear accelerator, using a (vendor provided) mechanical phantom that simulates breathing motion of the reflective marker. Before a patient simulation or treatment session, a brief system check is performed with the mechanical phantom to confirm correct operation.

### Selection of Gate

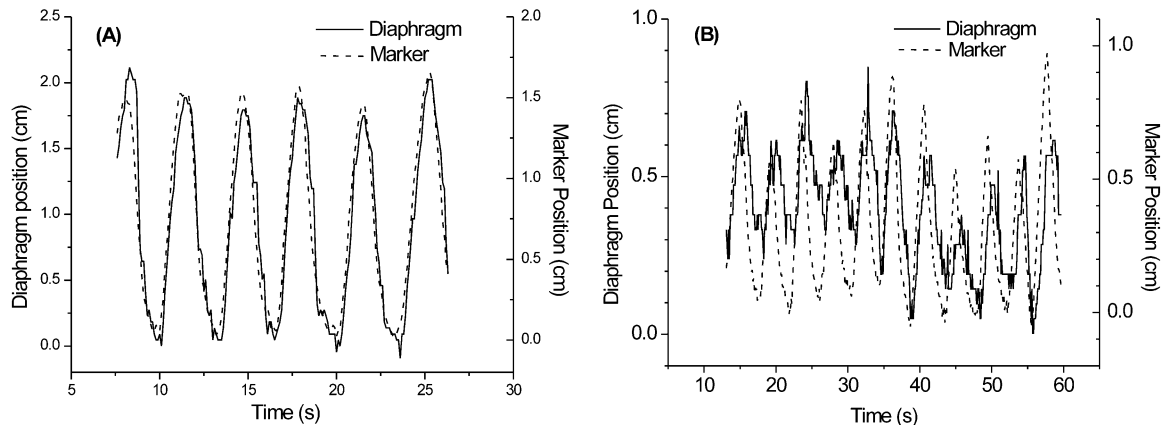
To minimize residual organ motion, gated treatment is usually centered at end expiration. Normal expiration during quiet breathing is a passive process during which the inspiratory muscles relax, resulting in a more reproducible anatomic

position at end expiration than at end inspiration. Gated treatment at end inspiration may offer an advantage for treatment of lung carcinoma because of the increased lung volume resulting in a lower dose to normal lung; however, preliminary studies comparing plans at 0% and 100% tidal volume have not shown significant benefit.<sup>27</sup>

The choice of gate width is a tradeoff between minimizing motion within the gate and completing treatment in a realistic time, usually a 20% to 40% duty cycle in our experience. There is little respiratory motion within a much narrower (ie, shorter duty cycle) gate. However, the beam delivery time is inversely proportional to the duty cycle. Overly long treatment times are inconvenient and may cause setup error because of motion of an uncomfortable patient. Treatment times may be reduced with higher dose rate; at MSKCC, gated treatment is normally delivered at 600 MU/min for both static and IMRT fields. Increasing the dose rate from 300 to 600 MU/min, while not halving the gated IMRT delivery time, does decrease it by approximately 60%. Kubo et al<sup>23,31</sup> have used a short (5-10 second) breath hold technique as a means of increasing the treatment duty cycle and reducing residual organ motion within the gate interval. Some centers have reported acquiring breath hold CT scans for simulation while allowing patient breathing during gated treatment, using the same respiration signal for both as a guide. However, the internal anatomy may differ significantly: transient changes of  $\sim 1$  cm in diaphragm or lung tumor position after the start of breath hold have been observed with fluoroscopy.<sup>3,32</sup>

### Accuracy of External Monitors in Gated Treatment

A key issue in gated treatment using external respiratory monitors is the accuracy of such monitors in predicting internal target organ position. The best correlation is expected from gating on a direct image of tumor motion, but this requires the invasive implantation of radio-opaque markers into the tumor<sup>20</sup> with attendant risks. A recent review of percutaneous lung biopsy procedures (comparable in risk to a percutaneous marker insertion) at MSKCC found that 23% of patients had postbiopsy pneumothorax, and of these, 7% required treatment (K Rosenzweig and A Covey, personal communication, March 2003).



**Figure 4.** Comparison of breathing waveform (marker) and diaphragm position versus time from a patient with (A) normal and (B) impaired diaphragm function.

Shirato et al<sup>33</sup> have reported that 3 out of 6 patients receiving bronchoscopic marker insertion into a central lung lesion experienced a dropping of the marker out of the lesion, whereas dropping occurred in 3 out of 41 bronchoscopic insertions into peripheral lesions.

Because the tumor is often not visible in fluoroscopy or portal radiographs and in the absence of implanted markers, one must rely on a readily discernible anatomic surrogate such as the diaphragm or anterior chest wall. The diaphragm likely correlates well with liver tumors; Dawson et al<sup>34</sup> found diaphragm position to correlate within approximately 0.2 cm with microcoils implanted near hepatic tumors. Correspondence of lung tumor motion with the diaphragm or chest wall is varied and should be measured for individual patients.<sup>3,35</sup> Fluoroscopic studies with the RPM system have shown high short-term (0.5-1 minutes) correlation between respiratory signal (abdominal wall motion) and diaphragm motion in most cases (Fig 4A).<sup>26,36</sup> In some cases, a diaphragm with impaired function may lag ~0.5 seconds with respect to the breathing waveform (Fig 4B); a corresponding delay in the beam gate may yield a modest (~15%) reduction in residual diaphragm motion during gated treatment. Internal/external correlation can be disturbed or lost completely by transient changes in breathing.<sup>37</sup> Drifts of the external signal may occur, caused by patient movement, particularly if the motion amplitude is small, such as monitoring anterior chest wall motion.<sup>32</sup> In the case of amplitude-based gating with the RPM system, a

drift of the waveform with respect to the thresholds can result in dose delivery occurring at points at an unintended part of the breathing cycle (ie, between end inspiration and expiration) (Fig 3A). Irregular breathing can adversely affect the quality of a CT scan triggered from the respiration waveform, causing slice acquisition at the wrong point of respiration and leading to motion artifacts in the images.

For these reasons, patient training is important to allow the patient to familiarize herself with the breathing technique and to evaluate the patient's ability to achieve reproducible respiratory signals. As mentioned earlier, audio and visual coaching may improve the performance of the RPM system<sup>23,36,38</sup>; the former can increase the regularity of the breathing period (Fig 3B), whereas the latter aids in reproducing the breathing amplitude. A study of the initial 6 patients with the RPM system at MSKCC found that average diaphragm excursion was reduced from 1.4 cm (range 0.7-2.1 cm) with uninstructed breathing and without gating to 0.3 cm (range 0.2-0.5 cm) with verbal breathing instruction and gated at end expiration for 25% of the breathing cycle. A second benefit is to decrease the incidence of beam hold-off from irregular breathing, thus decreasing treatment times. The effectiveness of audio/visual prompting is, of course, dependent on patient cooperation. Vedam et al<sup>26</sup> studied 5 patients with the RPM system and did not find audio/visual prompting to significantly improve the ability to predict diaphragm position from the respiratory signal during a treatment



session (ie, once the initial signal-to-diaphragm relationship for the session is known). The studies to date have involved limited numbers of patients, clearly pointing out the need for further investigation.

Another quality assurance issue involves ensuring the reproducibility of internal organ position between simulation and treatment. Although external monitors may correlate well with the respiratory organs within a single session, thus reducing intrafractional variations, the relationship between external monitor signal and internal organ positions may change between sessions, which can adversely affect organ reproducibility and give rise to interfractional variations. Factors that can affect the diaphragm/respiratory signal relationship between sessions include changes in patient's respiration pattern (eg, in the relative amount of chest vs abdominal breathing), changes in abdominal pressure (eg, stomach contents, ascites, or changes in hepatic tumor shape and size), and possible inaccuracies in the monitoring devices themselves. Interfractional diaphragm position variations have been observed in some instances to be larger than intrafractional ones. Ford et al<sup>39</sup> examined localization radiographs of 8 patients receiving respiration gated treatment during tidal breathing and separated the observed interfractional diaphragm variation into systematic (ie, mean displacement of the diaphragm from its planned position) and random (daily displacements about the mean) components. The mean  $\pm$  1 SD systematic variation for the patient group was  $0.00 \pm 0.39$  cm, whereas random variations were  $0.28 \pm 0.10$  cm (mean  $\pm$  1 SD of patient-specific  $\sigma$ ); intrafractional variation observed within the gated interval under fluoroscopy was  $0.26 \pm 0.17$  cm. The random interfractional and intrafractional variations were comparable in magnitude, whereas the systematic interfractional variations were larger. Our subsequent studies have found that in one third of patients, the diaphragm position on the radiographs showed a systematic displacement of at least 0.5 cm relative to its position on the digitally reconstructed radiograph constructed from the planning CT simulation. It is therefore essential to have a program of frequent gated portal radiographs of the surrogate organ (or target, if visible) throughout treatment to measure interfractional variations.

Imaging and quantification of tumor motion is important for determining appropriate PTV margins. When using a surrogate such as the diaphragm during treatment, the relative magnitudes of target and surrogate motion should be measured at least during simulation to infer the amount of target displacement for a given surrogate displacement. The standard approach has been to examine tumor motion under fluoroscopy.<sup>40</sup> Other techniques include repeat breath hold CT scans at different inspiration levels,<sup>3,7,25</sup> sequential CT images at a single slice,<sup>41</sup> and high speed MRI.<sup>42</sup> More recently, 4-dimensional CT capabilities correlated with respiration are becoming available, which provide 3D image sets at multiple points in the respiratory cycle<sup>43-45</sup> (see also the articles by George Chen and Paul Keall). It is important to keep in mind that the positional relation between tumor and surrogate may change over the treatment course, thus confirming interfractional constancy of surrogate position does not necessarily guarantee the same for the target.

## Future Directions

Recent advances in imaging technology provide a possible means of augmenting the reliability of external monitors for gated treatment. An active area of development is to obtain kilovoltage or megavoltage quality 3D image sets in the treatment room, using fan beam or cone beam geometries.<sup>46-50</sup> A 3D image set at the start of a treatment session could localize the target, correct for its position if necessary, and establish its positional relationship with the diaphragm or chest wall for use as a target surrogate in that session. During treatment, an external monitor would provide a real-time respiratory signal, whereas a combination kV x-ray source and detector could verify the position of the surrogate anatomy immediately before enabling the beam-enable gate. A key component to such image-guided approaches will be computer programs to automatically localize target and nontarget organs in the image sets, using the delineated organs in the planning CT as a guide, and taking organ deformation into account; so-called deformable image registration algorithms are an active area of investigation.<sup>50-52</sup>

## Conclusions

A common goal of the interventional strategies described here is to immobilize the tumor. For some disease sites, breath hold treatment with increased lung inflation can be of additional benefit in sparing organs at risk. A word of caution is in order with regard to reducing treatment margins. Intrafractional and interfractional target variations should be measured and taken into account through a program of imaging at simulation and treatment. Consideration also must be given to other factors that can contribute to target underdose, including uncertainty in defining the extent of the clinical target volume, patient setup errors, and for lung tumor, the increased beam penumbra and dose buildup in lung tissue.

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