Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2007 April 1; 67(5): 1548–1558.

Observation of interfractional variations in lung tumor position using respiratory gated and ungated megavoltage cone-beam CT

Jenghwa Chang, Ph.D.¹, Gig S. Mageras, Ph.D.¹, Ellen Yorke, Ph.D.¹, Fernando De Arruda, M.D.², Jussi Sillanpaa, Ph.D.¹, Kenneth E. Rosenzweig, M.D.², Agung Hertanto, Ph.D.¹, Hai Pham¹, Edward Seppi, Ph.D.³, Alex Pevsner, Ph.D.¹, C. Clifton Ling, Ph.D.¹, and Howard Amols, Ph.D.¹

¹Medical Physics, Memorial Sloan Kettering Cancer Center

²Radiation Oncology, Memorial Sloan Kettering Cancer Center

³Ginzton Technology Center, Varian Medical Systems

Abstract

Purpose/Objective—To evaluate the use of megavoltage cone-beam CT (MV CBCT) to measure interfractional variation in lung tumor position.

Materials/Methods—Eight non-small-cell lung cancer patients participated in the study, 4 non-gated and 4 using respiratory gating. All patients received a MV CBCT scan at weekly intervals. Contoured planning CT and MV CBCT images were spatially registered based on vertebral anatomy, and displacements of the tumor center of mass (COM) determined. Setup error was assessed by comparing weekly portal orthogonal radiographs with DRRs generated from planning CT images. Hypothesis testing was performed to test the statistical significance of the volume difference, COM displacement, and setup uncertainty.

Results—The vertebral bodies and soft tissue portions of tumor within lung were visible on the MV CBCT scans. Statistically significant systematic volume decrease over the course of treatment was observed for one patient. The average COM displacement between simulation CT and MV CBCT scans were 2.5mm, −2.0mm and −1.5 mm with standard deviations of 2.7mm, 2.7mm, and 2.6 mm in the right-left, anterior-posterior and superior-inferior directions. The mean setup errors were smaller than the COM shifts, while the standard deviations were comparable. In most cases, the MV GTVs are located on average at least 5 mm inside the CT GTV expanded by 10mm.

Conclusions—MV CBCT can image lung tumors and may prove valuable for image-guided radiotherapy. Our conclusions must be qualified in view of the small patient number.

Keywords

Mega-voltage CBCT; respiratory gating; image-guided radiotherapy; setup verification; interfractional variation

Correspondence: Jenghwa Chang, Ph.D. Memorial Sloan-Kettering Cancer Center Medical Physics Department 1275 York Avenue New York, NY 10021, USA TEL: 212-639-6036 Email: changj@mskcc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Accurate patient setup is crucial for high-precision radiotherapy (RT). Current standard practice involves weekly comparison of 2D portal images with reference images (digitally reconstructed radiographs (DRR) or simulation films), based primarily on the matching of bony anatomy. However, identification and alignment of objects on 2D projection images is challenging and prone to error for certain treatment sites and beam directions. Also, the tumor is often not visible in 2D portal images, even in regions of high anatomic contrast such as the lung^{1, 2}. In addition, significant intra- and inter-fractional organ motion can make it difficult to determine the accuracy of dose delivered.

Over the last few years, use of on-board three-dimensional (3D) tomographic imaging systems, such as helical megavoltage computed tomography (MV CT)³, kilovoltage cone beam CT (kV CBCT)^{4, 5} and megavoltage cone-beam computed-tomography (MV CBCT)⁶⁻⁹, have been studied to improve setup accuracy by acquiring relevant 3D anatomic information with the patient in treatment position. Several reports describe the clinical evaluation and application of these imaging systems. Smitsmans et al.¹⁰ studied the combined use of kV CBCT and a 3D image registration algorithm and reported errors in gray-value registration ranging from 1.0 to 2.4 mm (1SD). Letourneau et al.¹¹ used a kV CBCT system for online setup of eight patients with implanted gold markers in the prostate, and achieved a residual error of ± 1.5 mm. Langen et al.¹² performed a similar study on three prostate patients (112 alignments) using a helical MV CT system and demonstrated that the alignment differed by ≥ 3 mm in 3%, 6% and 3% of all registrations in the anterior-posterior, superior-inferior, and lateral directions. Mahan et al.¹³ used a similar system to set up 8 patients to within 1.2 mm of the planned positions for the treatment of spinal metastasis without stereotactic immobilization.

Lung cancer is the leading cause of cancer deaths in the United States¹⁴, and NSCLC accounts for approximately 80% of lung cancers¹⁵. Two-year local control is 30-50% for medically inoperable stage I-II NSCLC tumors treated with RT and 15-20% for locally advanced disease¹⁶. Several studies have shown that higher radiation doses correlate with improved local control¹⁷⁻¹⁹. However, treatment dose is limited by the dose-volume constraints of normal lung^{20, 21}. Enlarging the gross target volume (GTV) to a clinical target volume (CTV) and planning target volume (PTV) adequate to account for respiration-induced motion, severely limits dose escalation in many patients. Kupelian et al.²² scanned 10 patients with non-small-cell lung cancer (NSCLC) with a helical MV CT during external beam RT, and reported an average daily tumor volume decrease rate of 1.2%. Siker et al.²³ used a similar device to study 25 NSCLC patients. They reported that 68% of the patients have stable disease (volume shrinkage less than 25% after treatment completion) and only 32% show the more dramatic shrinkage seen in the Kupelian series²². At our institution, a clinical trial of the Memorial Sloan-Kettering Cancer center (MSKCC) MV CBCT system is also ongoing for NSCLC patients.

Traditionally, a generic CTV to PTV expansion is used to assure CTV coverage. However, recent developments in gated CT and 4D CT allow the treatment target to be isolated in a less mobile phase of the breathing cycle for radiation treatment using respiration control methods, such as breath-hold^{24, 25}, gating²⁶⁻²⁹, and target tracking^{30, 31}. Although respiration control methods may permit PTV reduction, the amount of reduction is not well established and needs to be individually quantified. Additionally, since most respiration control methods use a surrogate such as implanted radio-opaque fiducials^{32, 33}, diaphragm, or chest wall^{34, 35} to generate the gating or tracking signal and monitor treatment accuracy, the validity of these surrogates for lung tumor position also needs confirmation. On-board imaging of the patients in the treatment position could be an excellent tool for determining and monitoring the adequacy of CTV coverage over the course of treatment.

In this study, we report the use of MV CBCT for observing interfractional variation to determine the adequacy of CTV coverage for 8 NSCLC patients at our institution. Four gated and four non-gated patients (nine lesions), were scanned approximately weekly using the MSKCC MV CBCT system. The volume, location (centroid of the tumor relative to the bony anatomy) and directional displacement of the tumors were analyzed over the course of their radiation treatment. Setup error was also calculated and compared with the variation in tumor location.

2. Materials and Methods

MV CBCT system

The MSKCC MV CBCT system^{8, 9} is composed of a Varian 2100EX linear accelerator (LINAC), an image detector, an external synchronization circuit, and a respiratory gating system. The image detector consists of a 9 mm thick crystalline CsI scintillator on top of an array of aSi photodiodes, with an active area of 39.7×29.8 cm² and a maximum frame rate of 30 frames/s. The external synchronization circuit limits the dose to one beam pulse per image and synchronizes the detector readout with the radiation delivery. The respiratory gating system (“Real-time Position Management” or RPM, Varian Medical Systems) uses an infrared camera to track a reflective marker on the patient's abdomen and enables the LINAC beam during treatment only when the marker is within a user-specified window.

During a CBCT session, the detector is mounted at 148 cm from the source, offset laterally by ~8 cm to expand the axial field of view (FOV) from 29.8 cm to 37 cm. A 360° gantry rotation is required for tomographic reconstruction in this configuration. For non-gated scans the gantry moves continuously and the detector acquires single-pulse projection images at a rate of 7.5 frames per second. CBCT acquisition requires 1 minute, which is limited by the maximum gantry rotation speed. One full rotation results in 450 acquired projections, and a dose of 13 MU/12 cGy to the patient.

In a previous study⁸, continuous gantry rotation was utilized with projections acquired only when the measured respiratory motion was within a user-defined gating threshold. This resulted in image degradation due to gaps in the data. A “gated rotation-continuous acquisition” method⁸ was developed where the gantry motion stopped/started as the respiratory trace exited/entered the gating threshold. This improved image quality, but produced excessive vibration that might damage the gantry clutch. In the current study, an improved technique was devised to reduce both effects by synchronizing image acquisition and gantry rotation using the RPM system. In this method, the LINAC is operated in the research “dynamic beam delivery” (DBD) mode, controlled by the RPM system and a user-specifiable script⁶. The script consists of 40 segments, each of 9° rotation with simultaneous delivery of imaging dose. Special synchronization circuitry built for this purpose initiates the execution of one segment upon receiving a trigger from the RPM system at the start of a gate. Each segment takes 1.5 s and corresponds to a gate at end expiration of the same duration. The LINAC then pauses and waits for another RPM trigger to execute the next segment. The imaging duty cycle is 20-25% and the complete 360° image acquisition takes 3 to 4 minutes. The image acquisition system acquires images continuously, but discards blank images acquired between segments, i.e., those having pixel intensities below a preset threshold. Beam-on time and the number of images used in volume reconstruction are the same as for ungated acquisition (13 MU/12 cGy, about 450 images); however, the images are uniformly spaced over 360°, yielding better quality volume reconstructions with reduced artifacts from respiratory motion or non-uniform spacing.

Clinical Methods

Eight patients receiving radiation therapy for NSCLC participated in this study (approved by the institutional review board). Table 1 lists their demographics, including tumor histology, location and stage, as well as treatment dose, technique (gated or non-gated), and number of beams. Because image contrast with the MV CBCT system is inadequate to discriminate mediastinal lesions, each patient was required to have part of the gross target volume (GTV) visible as a soft-tissue mass that contrasted with surrounding low-density lung. A total of nine lesions were imaged and analyzed (one patient had a right upper lobe lesion and a left lower lobe lesion). All patients were immobilized supine in a custom alpha cradle, received a simulation CT scan (Model PQ 5000 AcQSim, Marconi/Philips Medical Systems, Cleveland OH), and were treated and imaged on the same LINAC (Varian 2100 EX). Four (patients 5-8) were simulated and treated with respiratory gating around end-expiration using the Varian RPM system.

The simulation CT scan was performed 1-2 weeks before the first treatment. The slice thickness was 3mm and the gantry rotation speed was 1 slice per second. The non-gated patients received helical scans without special breathing instructions, while the gated patients received amplitude-gated axial scans around end-exhale per RPM for a ~30% duty cycle, corresponding to a diaphragm motion of 5-7 mm (assessed under fluoro). The breathing periods for these patients were 4-6 sec. All cases were treated with 6 MV photons, 2 Gy per fraction using multiple IMRT co-planar beams. The field arrangements were customized to the patient (varied from 3 beams per tumor to 7 as shown in Table 1) by the planner with the aim of meeting departmental normal tissue tolerance requirements (maximum cord dose < 50 Gy, Lyman model lung normal tissue complication probability $\leq 25\%$) and a general departmental guideline to keep the dose to the contralateral lung low. The time from first to last beams is usually less than 5.5 minutes.

The first MV CBCT scan was usually performed at the 2nd treatment week in order not to overburden the patients with CBCT imaging in the first week. For each imaging session, MV CBCT images were acquired shortly before or after a treatment session, at 1-2 week intervals scheduled to span the patient's treatment course. Four or 5 MV CBCT image sets were acquired for each patient. Prior to MV CBCT imaging, the patients were set up as for treatment and isocentric orthogonal localization radiographs were acquired. Subsequently, the couch was translated to place isocenter at patient midline and mid-depth to ensure that the gantry would clear couch and patient during 360 degree rotation. This shift also minimized artifacts from tissues that were outside the field of view but contributed signal for reconstruction. Longitudinal shift was also performed in some cases to include the most relevant anatomy in the MV CBCT scan. Four of the 5 cone-beam acquisitions of patient 5 and all cone-beam acquisitions for patients 6, 7 and 8 were synchronized with respiratory gating. The single ungated scan for patient 5 was not included in the data analysis.

Image registration

Customized software was developed to combine manual and automatic rigid registration between MV CBCT and planning CT images. The automatic registration implements a mutual information algorithm and can be applied to a user-selected region of interest (ROI). The user can choose cut planes (transverse, sagittal, coronal) to evaluate and fine-tune the registration by manually translating or rotating one image set rigidly with respect to the other.

The registrations focused on alignment of the spine, as other anatomical features were often affected by respiratory motion and required deformable registration. Thoracic spine, on the other hand, is in approximately the same position since all the patients were immobilized in their treatment alpha cradle for all imaging sessions. The ROI registration was first performed

on a narrow volume including the full length of the spine imaged on the MV CBCT and CT scans. The registration was then fine-tuned using the manual tool on the sagittal and coronal planes through the spine to optimize the matching of intervertebral spaces, any spinal curvature, small calcifications on the edges of vertebral bodies, and shape of vertebral bodies in the transverse views. Repeat registrations were done one month apart for one MV CBCT scan for each patient to assess registration consistency.

The same physician delineated the GTV on all planning CT and MV CBCT images. The physician first delineated the portion of the GTV visible as a high-contrast feature within lung on each planning scan, using the same window and level display settings for all cases. Below, we refer to this sub-volume as the “CT GTV”. Window and level display settings for each registered MV CBCT were chosen to obtain visual similarity of ipsilateral lung structures with the planning CT. The planning scan was then used as a guide for delineating the corresponding “MV GTV” on each MV CBCT image set. To test intra-observer variation, the physician re-contoured the “MV GTV” on one MV CBCT scan for each of three patients without reference to the first MV CBCT contours. The differences between original and repeat MV GTV surfaces were analyzed by measuring the directional displacement between two target volumes (described below in “Data Analysis”).

Note that the GTVs drawn in this study were different from the CTVs contoured by the treatment physician because the latter included lung with possible microscopic extension. The actual clinical PTV margin varied from 10 to 17 mm for these patients as the treatment physician's practice is to edit the computer-generated 3D PTV expansion. For purposes of consistency in this analysis, a volume referred to as “GTV10” was used as a surrogate for the PTV. This was generated by a 3D expansion of the CT GTV by 10 mm³⁶. Since previous studies (Mechalakos et al³⁷ and references therein) have reported that mean respiration-induced intra-fractional lung tumor motion is around 10 mm, the choice of 10 mm is a yardstick for comparing inter-fractional motion observed in our study relative to typical magnitude respiration-induced motion.

Data Analysis

We developed customized software that enabled calculation of the GTV volume (cc) delineated on each image set and the 3-dimensional displacement of its centroid relative to the registered planning scan. Additionally, a software tool adapted from Remeijer et al.³⁸ was used for a more detailed study of the directional dependence of GTV displacement³⁹. Briefly, the algorithm calculates the distance between the MV GTV surface on the registered MV CBCT scan and the GTV10 surface along different directions. It does so by casting rays radially outward from the MV GTV centroid, finding the intersection with the GTV10 surface along the ray, then finding the closest distance to the MV GTV boundary in 3D. The results are plotted as 2D maps of polar angles theta and phi, analogous to Mercator maps of the earth. Theta=0 (180) is in superior (inferior) direction, while theta=90 and phi=90 (phi=270) is in the posterior (anterior) direction. Results from the set of MV CBCT scans of each patient are analyzed and combined to form a composite 2D map of mean and closest MV GTV-to-GTV10 distance along each direction.

Setup error is not included in the above analysis because the image sets are registered according to spinal anatomy. To assess the additional impact of setup error, orthogonal radiographs, acquired weekly as part of the normal clinical process, were compared with the corresponding DRRs from the planning CT images, using an in-house contour-matching program. A physicist outlined vertebral bodies and other structures on the DRRs and transferred those contours onto a portal radiograph. These contours were translated to get the best match with corresponding anatomical structures visible on the radiograph. The setup error is the distance between these

contours in the DRR and the radiograph. The average treatment course is 6 weeks; hence approximately 6 setup error determinations were made for each patient.

Statistical Analysis

We used hypothesis testing to evaluate if any systematic changes in setup or center-of-mass (centroid) position of the MV GTV were present over the course of radiotherapy. Assuming the quantities of interest were a random sample of n observations (e.g., five scans) from a normal population with mean μ and variance σ^2 , the following two hypotheses were tested

$$\mathcal{H}_0 : \mu = 0 \text{ versus } \mathcal{H}_1 : \mu \neq 0, \quad (1)$$

where $\mathcal{H}_0 : \mu = 0$ indicates μ is not statistically significantly different from 0, and $\mathcal{H}_1 : \mu \neq 0$, implies that the change is statistically significant. We use the following confidence interval for this test,

$$\left(\bar{x} - t_{(1-\alpha/2, n-1)} \delta / \sqrt{n}, \bar{x} + t_{(1-\alpha/2, n-1)} \delta / \sqrt{n} \right), \quad (2)$$

where $\bar{x}$ is the sample mean, δ^2 the sample variance, α the significance level, and $t_{(1-\alpha/2, n-1)}$ the $(1-\alpha/2)$ -quantile of a t distribution with $n-1$ degrees of freedom. Hypothesis $\mathcal{H}_0$ was accepted only if the confidence interval in Eq. (2) contained 0. A 5% significant level was used in the tests, corresponding to a 95% confidence level.

To compare the tumor reduction rate with that published by Kupelian et al.²², linear regression was performed to find the best linear fit for the MV CBCT volume versus the treatment time (elapsed day since the start of treatment). The slope of this line (in % per day) is the rate of volume change (positive for increase and negative for reduction) over the course of treatment. We also tested the hypothesis that the slope is statistically significantly different from zero using the following confidence interval

$$\left(\hat{b}_1 - t_{(1-\alpha/2, n-2)} \sqrt{\text{var}[\hat{b}_1]}, \hat{b}_1 + t_{(1-\alpha/2, n-2)} \sqrt{\text{var}[\hat{b}_1]} \right), \quad (3)$$

where $\hat{b}_1$ is the estimated slope from the linear regression analysis and $\text{var}[\hat{b}_1]$ is the estimated variance of $\hat{b}_1$.

3. Results

The mean and standard deviation of the differences between the original and repeat MV GTV surfaces from the intra-observer variation test were respectively 0.2mm and 1.2 mm for the three MV CBCT scans selected in this study, indicating minimal intra-observer variation in contouring MV GTV. The registrations between the planning CT scan and multiple MV CBCT scans were also quite reproducible. On average, the first and repeat registrations agreed within better than 1 mm for all patients. The maximum differences in shifts required to register were 0.8 mm, 2.2 mm and 1.1 mm in the right-left (RL), anterior-posterior (AP) and superior-inferior (SI) directions, respectively.

The left-hand panels of Figure 1 depict the “CT GTV” (in green) of a right lung NSCLC for patient #1 in the axial, sagittal, and coronal planes of the planning CT scan. These contours have been transferred to one of this patient's MV CBCT scans (right-hand panels) using the spinal column registration method described above. Shown in white on the MV CBCT scans are the MV GTV contours, which were then transferred to the planning CT scans. A small displacement between the CT GTV and MV GTV is evident. Although the quality of the planning CT and the MV CBCT images appears different, the vertebral features used for registration with the planning CT scan as well as the GTV are clearly visible in the MV CBCT image.

Figure 2A shows the variation in CT GTV volume (scan 0) and MV GTV volumes (scans 1-5). The mean percent change in MV GTV volume relative to plan for each patient is given in the column “Chg” in the legend. Figure 2B shows the slope (shaded bar) of the linear regression analysis of the MV CBCT volume change over the course of treatment. The error bars are the 95% confidence interval for testing whether the slope is different from zero. The data, presented as the daily percent change relative to the volume of the first scan, ranges from 0.2% per day to -1.0% per day, with a mean of -0.3% per day and a standard deviation of 0.3% per day. Statistically significant volume reduction over the course of treatment is observed only for Patient #7.

There is a more pronounced volume difference between the planning CT and MV CBCT scans, as shown in Figure 2A. We attribute most of these observed volume changes between simulation and treatment to the difference in image quality and to differences between breathing induced artifacts (distorting^{40, 41} or blurring^{5, 8} the moving tumor) which result in contouring differences between the MV CBCT and the planning CT. However, the possibility of tumor shrinkage due to the radiation treatment in the first week cannot be ruled out, since MV CBCT scans were not acquired at the beginning of the treatment.

Figure 3 shows the average over the MV CBCT scans of the centroid displacements relative to the planning scan in (A) RL, (B) AP, and (C) SI directions for each tumor. Negative displacement in the RL, AP, or SI direction denotes that the average position of the MV CBCT GTV centroid is to the right, anterior, or inferior of the planning scan centroid. Error bars are the 95% confidence interval for testing non-zero average (or systematic) displacement. Statistically significant displacement was observed for 4, 3, and 4 lesions in the RL, AP, and SI directions, respectively. Figure 3D plots the average length and standard deviation of the total 3D centroid displacement for each patient. For each MV CBCT scan, the length of the centroid displacement is defined as $(RL^2 + AP^2 + SI^2)^{1/2}$. For only 3 of the 9 GTVs was the 3D displacement of the GTV centroid (averaged over all MV CBCT imaging sessions) less than 0.5 cm; for 4 GTVs, including patients #5 and #8, who were imaged with respiratory gating, the average displacement exceeded 0.6 cm. For patients #4, #5 and #8 the maximum centroid displacement exceeded 1 cm.

Figure 4 shows the mean setup error for the eight patients in (A) RL, (B) AP, and (C) SI directions, as measured from orthogonal portal images. Error bars are the 95% confidence interval for testing non-zero average (or systematic) setup error. Positive RL, AP, or SI means anatomy on the orthogonal radiograph needed displacement to the left, posterior, or superior to match the DRR. The largest difference between a pair of registrations (in one direction) was 4.7 mm. Three of 16 re-registrations had differences exceeding 4 mm. Most of the mean setup errors are not statistically significantly different from zero. Figure 4D compares (mean over the 8 patients and one standard deviation) the displacement of GTV centroid and the setup error. The mean setup errors are smaller than the mean GTV centroid shifts in all three dimensions, while the standard deviations are comparable. The smaller mean setup error is expected because the clinical radiograph-based setup correction protocol matches the bony anatomy (vertebral bodies) in portal images and DRRs to correct for laser misalignment and procedural differences between simulation and setup that may systematically displace the vertebral bodies and significantly deviate the mean setup error⁴². This correction protocol, however, does not correct the GTV centroid shift relative to the bony anatomy.

Figures 5 and 6 illustrate the results of the directional distance analysis for patients #4 (non-gated) and #8 (gated), who have the most significant directional shift between the MV GTV and the GTV10. Results of the directional distance analysis for other lesions are not shown here because in most cases, the MV GTVs are located on average at least 5 mm inside the GTV10, indicating that the MV GTVs were well covered by GTV10. The plot of mean MV

GTV-to-GTV10 distance in Figure 5(a) indicates a systematic anterior-inferior displacement of 0.5 to 0.8 cm (dependent on direction) for patient 4. This is confirmed by examination of sagittal sections of MV CBCT scans 1 through 4, in Figures 5(e) through 5(h), which show the contour overlay of the MV GTV (blue) and CT GTV (red). The plot of the closest MV GTV-to-GTV10 distance in Figure 5(b) shows that the MV GTV extends outside the GTV10 in the anterior-inferior direction. This occurs in MV CBCT scan 4, as observed in Figures 5(d) and 5(h).

Patient #8 received gated treatment, with planning CT and all MV CBCT sessions gated. The plot of mean MV GTV-to-GTV10 distance in Figure 6(a) shows a systematic anterior displacement of about 0.5 cm. MV GTV displacement in individual scans exceeded 1 cm but varied in direction over the treatment course. In scan 1 the MV GTV is displaced anteriorly and superiorly (Figures 6c and 6e), while in scan 5 it is displaced left, anteriorly, and inferiorly (Figures 6d and 6f). Thus the mean displacement in a particular direction of Figure 6(a) can be less than on any single scan. The plot of worst (closest) MV GTV-to-GTV10 distance (Figure 6b) shows that the GTV exceeded the GTV10 in two regions, reflecting the varying direction of displacement in the different scans. Note that the patient's chest in the MV CBCT is expanded anteriorly by 1-1.5 cm (depending on location and date of MV scan) relative to the planning CT (arrow in Figure 6c), causing the GTV to displace anteriorly. However, because the average MV GTV volume of patient #8 is 40% smaller relative to the CT GTV, the amount of MV GTV protruding outside GTV10 (Figure 6b) is smaller than for patient #4 (Figure 5b) even though the MV GTV centroid displacement of Patient #8 is larger (Figure 3).

4. Discussion

There are two major concerns in using an MV source for tomographic imaging for image-guided radiotherapy: high imaging dose and whether the soft tissue contrast is adequate to delineate tumor and critical organs. In this paper we demonstrate that MV CBCT is feasible for setup verification of NSCLC patients as the lesions and bony anatomy were clearly visible on the scan (Figures 1, 5 and 6). The dose (~12 cGy to isocenter) for each MV CBCT scan is comparable to weekly portal imaging. While this is higher than the dose (less than 3 cGy to isocenter) for kV CBCT, it could be further reduced with better engineering of the MV CBCT system. For example, we are investigating acquiring projection images with a fraction of a beam pulse instead of a single beam pulse to acquire projection images, which will cut the imaging dose by a factor of 2-3.

Unlike the study by Kupelian et al.²² who reported an average 1.2% daily decrease in tumor volume, we observed no time trend in tumor volume reduction during the treatment course. As shown in Figure 2, the average decrease rate for MV GTV is 0.3% per day; only Patient #7 demonstrated statistically significant volume reduction over the treatment course. These data are more consistent with the findings of Siker et al.²³ who reported that 68% of the patients had stable disease (tumor volume shrinkage less than 25% after treatment completion). It is not clear why different tumor shrinkage patterns were observed but there were differences in patient selection and treatment regimen between these two studies. In the Kupelian series²², over half of the patients had squamous cell carcinoma, while in this study most of the patients had adenocarcinoma (Table 1), which might shrink more slowly than squamous cell carcinoma. Additionally, response of recurrent tumors (patients #2 and #7) may be substantially different from those receiving their first course of radiotherapy because the recurrent tumor mass may be more radio-resistance.

We have used conventional portal radiographs to assess changes in diaphragm position as a surrogate for tumor position³⁴ and concluded that interfractional internal anatomic displacement can be significant for gated patients, and can take the form of day-to-day changes

in offset and/or systematic displacement³⁴. Day-to-day offset changes are independent of the imaging and treatment techniques and might result in similar mean and SD of the centroid displacement for gated and non-gated patients (Figure 3). Systematic displacement was observed for Patient #8 (gated), whose internal anatomical breathing pattern was different at treatment than at simulation, although treatment and simulation RPM breathing traces were fairly consistent. As shown in Figure 6, a larger than 1 cm anterior expansion of the chest wall was observed and was seen in all five MV CBCT scans. If dose and time permitted, more frequent CB imaging could monitor both day-to-day variation and systematic interfractional uncertainty and rational corrective measures could be taken. These could be combined with gating to minimize both inter and intra-fractional uncertainty for mobile tumors.

Intra-fraction motion causes motion artifacts, resulting in blurred images for MV CBCT^{5,8}, and distorted images on simulation CT scans^{40, 41}. Although these artifacts have minimal effect on the registration of bony landmarks (e.g. spine), they degrade visualization of contrast changes and cause contouring error which adversely affects measurement accuracy of tumor extent and volume. Similar motion artifacts were also observed on kV CBCT, as the temporal sequence of both imaging techniques are similar despite the difference in x-ray source energy. Motion artifacts should be minimized for the best use of CBCT for image-guided patient setup. Although gated CT and CBCT have been shown to reduce motion artifacts, gated imaging can not completely eliminate motion artifacts due to residual organ motion^{41, 43, 44} within the imaging gate. Irregular patient breathing also causes artifacts in both CT and CBCT, as it results in either slices or projection images at the wrong phase of the breath cycle. Minimization of respiratory motion effects during tomographic imaging is an ongoing area of research, and the optimal techniques for achieving this have yet to be determined.

We note that our MV CBCT system is a prototype, not approved for routine image-guided setup. Our directional analysis (Figures 5 and 6) using a GTV plus 10 mm margin (GTV10) indicates that two patients had GTVs partially outside GTV10 for at least one scan. Clinical availability of a MV CBCT would allow identification and correction of the isocenter position or change of PTVs and treatment plans for patients with large GTV displacements.

In conclusion, this study demonstrates that MV CBCT can image lung tumors for both gated and non-gated patients and may prove valuable for image guided radiotherapy. The imaged tumors demonstrated significant interfractional COM displacements. Setup error has zero mean but similar standard deviation as the COM displacement. Our conclusions must be qualified in view of the small patient number.

Acknowledgments

Part of this paper was presented in the 47th ASTRO annual meeting, October 16-20, 2005, in Denver, Colorado. The work at MSKCC was supported in part by NIH grant P01-CA59017. Hardware and software development at Varian was supported in part by grants from the Henry M. Jackson Foundation and the Walter Reed Army Medical Center.

5. References

1. Erridge SC, Seppenwoolde Y, Muller SH, et al. Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer. *Radiotherapy and Oncology* 2003;66:75–85. [PubMed: 12559524]
2. Ford EC, Mageras GS, Yorke E, et al. Evaluation of respiratory movement during gated radiotherapy using film and electronic portal imaging. *International Journal of Radiation Oncology Biology Physics* 2002;52:522.
3. Mackie TR, Kapatoes J, Ruchala K, et al. Image guidance for precise conformal radiotherapy. *International Journal of Radiation Oncology Biology Physics* 2003;56:89–105.

4. Jaffray DA, Siewerdsen JH, Wong JW, et al. Flat-panel cone-beam computed tomography for image-guided radiation therapy. *International Journal of Radiation Oncology Biology Physics* 2002;53:1337–1349.
5. Sonke J-J, Zijp L, Remeijer P, et al. Respiratory correlated cone beam CT. *Medical Physics* 2005;32:1176–1186. [PubMed: 15895601]
6. Sillanpaa J, Chang J, Mageras G, et al. Developments in megavoltage cone beam CT with an amorphous silicon EPID: Reduction of exposure and synchronization with respiratory gating. *Medical Physics* 2005;32:819–829. [PubMed: 15839355]
7. Pouliot J, Chen J, Aubin M, et al. Low-dose megavoltage cone-beam CT for radiation therapy. *International Journal of Radiation Oncology Biology Physics* 2005;61:552–560.
8. Chang J, Sillanpaa J, Ling CC, et al. Integrating respiratory gating into a megavoltage cone-beam CT system. *Medical Physics* 2006;33:2354–2361. [PubMed: 16898437]
9. Sillanpaa J, Chang J, Mageras G, et al. Low-dose megavoltage cone-beam computed tomography for lung tumors using a high-efficiency image receptor. *Medical Physics* 2006;33:3489–3497. [PubMed: 17022245]
10. Smitsmans MHP, De Bois J, Sonke J-J, et al. Automatic prostate localization on cone-beam CT scans for high precision image-guided radiotherapy. *International Journal of Radiation Oncology Biology Physics* 2005;63:975–984.
11. Letourneau D, Martinez AA, Lockman D, et al. Assessment of residual error for online cone-beam CT-guided treatment of prostate cancer patients. *International Journal of Radiation Oncology Biology Physics* 2005;62:1239–1246.
12. Langen KM, Zhang Y, Andrews RD, et al. Initial experience with megavoltage (MV) CT guidance for daily prostate alignments. *International Journal of Radiation Oncology Biology Physics* 2005;62:1517–1524.
13. Mahan SL, Ramsey CR, Scaperoth DD, et al. Evaluation of image-guided helical tomotherapy for the retreatment of spinal metastasis. *International Journal of Radiation Oncology Biology Physics* 2005;63:1576–1583.
14. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *Ca-A Cancer Journal for Clinicians* 2006;56:106–130. [PubMed: 16514137]
15. Parkin DM, Sankaranarayanan R. Overview on small cell lung cancer in the world: Industrialized countries, third world, Eastern Europe. *Anticancer Research* 1994;14:277–282. [PubMed: 8166467]
16. Ginsberg, R.; Vokes, E.; Rosenzweig, K. Non small cell lung cancer. In: Devita, V.; Hellman, S.; Rosenberg, S., editors. *Cancer: Principles and practice of oncology*. 6th ed.. Lippincott, Williams and Wilkins; Philadelphia: 2001. p. 925-982.
17. Cox JD, Azarnia N, Byhardt RW, et al. A randomized phase I/II trial of hyperfractional radiation therapy with total doses of 60.0 Gy to 79.2 Gy: Possible survival benefit with ≥ 69.6 Gy in favorable patients with radiation therapy oncology group stage III non-small-cell lung carcinoma: Report of Radiation Therapy Oncology Group 83-11. *Journal of Clinical Oncology* 1990;8:1543–1555. [PubMed: 2167952]
18. Narayan S, Henning GT, Ten Haken RK, et al. Results following treatment to doses of 92.4 or 102.9 Gy on a phase I dose escalation study for non-small cell lung cancer. *Lung Cancer* 2004;44:79–88. [PubMed: 15013586]
19. Rengan R, Rosenzweig KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. *International Journal of Radiation Oncology Biology Physics* 2004;60:741–747.
20. Yorke ED, Jackson A, Rosenzweig KE, et al. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. *International Journal of Radiation Oncology Biology Physics* 2005;63:672–682.
21. Seppenwoolde Y, Lebesque JV. Partial irradiation of the lung. *Seminars in Radiation Oncology* 2001;11:247–258. [PubMed: 11447582]
22. Kupelian PA, Ramsey C, Meeks SL, et al. Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: Observations on tumor regression during treatment. *International Journal of Radiation Oncology Biology Physics* 2005;63:1024–1028.

23. Siker ML, Tome WA, Mehta MP. Tumor volume changes on serial imaging with megavoltage CT for non-small-cell lung cancer during intensity-modulated radiotherapy: How reliable, consistent, and meaningful is the effect? *International Journal of Radiation Oncology Biology Physics* 2006;66:135–141.
24. Wong JW, Sharpe MB, Jaffray DA, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. *International Journal of Radiation Oncology Biology Physics* 1999;44:911–919.
25. Rosenzweig KE, Hanley J, Mah D, et al. The deep inspiration breath-hold technique in the treatment of inoperable non-small-cell lung cancer. *International Journal of Radiation Oncology Biology Physics* 2000;48:81–87.
26. Ohara K, Okumura T, Akisada M, et al. Irradiation synchronized with respiration gate. *International Journal of Radiation Oncology Biology Physics* 1989;17:853–857.
27. Kubo HD, Hill BC. Respiration gated radiotherapy treatment: A technical study. *Physics in Medicine and Biology* 1996;41:83–91. [PubMed: 8685260]
28. Kini VR, Vedam SS, Keall PJ, et al. Patient training in respiratory-gated radiotherapy. *Medical Dosimetry* 2003;28:7–11. [PubMed: 12747612]
29. Giraud P, Yorke E, Ford EC, et al. Reduction of organ motion in lung tumors with respiratory gating. *Lung Cancer* 2006;51:41–51. [PubMed: 16198022]
30. Keall PJ, Kini VR, Vedam SS, et al. Motion adaptive x-ray therapy: A feasibility study. *Physics in Medicine and Biology* 2001;46:1–10. [PubMed: 11197664]
31. Murphy MJ. Tracking Moving Organs in Real Time. *Seminars in Radiation Oncology* 2004;14:91–100. [PubMed: 14752737]
32. Imura M, Yamazaki K, Shirato H, et al. Insertion and fixation of fiducial markers for setup and tracking of lung tumors in radiotherapy. *International Journal of Radiation Oncology Biology Physics* 2005;63:1442.
33. Shirato H, Harada T, Harabayashi T, et al. Feasibility of insertion/implantation of 2.0-mm-diameter gold internal fiducial markers for precise setup and real-time tumor tracking in radiotherapy. *International Journal of Radiation Oncology Biology Physics* 2003;56:240.
34. Yorke E, Rosenzweig KE, Wagman R, et al. Interfractional anatomic variation in patients treated with respiration-gated radiotherapy. *Journal of applied clinical medical physics* 2005;6:19–32. [PubMed: 15940209]
35. Eccles C, Brock KK, Bissonnette JP, et al. Reproducibility of liver position using active breathing coordinator for liver cancer radiotherapy. *International Journal of Radiation Oncology Biology Physics* 2006;64:751–759.
36. Stroom JC, Storchi PRM. Automatic calculation of three-dimensional margins around treatment volumes in radiotherapy planning. *Physics in Medicine and Biology* 1997;42:745–755. [PubMed: 9127450]
37. Mechalakos J, Yorke E, Mageras GS, et al. Dosimetric effect of respiratory motion in external beam radiotherapy of the lung. *Radiotherapy and Oncology* 2004;71:191–200. [PubMed: 15110453]
38. Remeijer P, Rasch C, Lebesque JV, et al. A general methodology for three-dimensional analysis of variation in target volume delineation. *Medical Physics* 1999;26:931–940. [PubMed: 10436894]
39. Pevsner A, Davis B, Joshi S, et al. Evaluation of an automated deformable image matching method for quantifying lung motion in respiration-correlated CT images. *Medical Physics* 2006;33:369–376. [PubMed: 16532942]
40. Balter JM, Ten Haken RK, Lawrence TS, et al. Uncertainties in CT-based radiation therapy treatment planning associated with patient breathing. *International Journal of Radiation Oncology Biology Physics* 1996;36:167–174.
41. Chen GTY, Kung JH, Beaudette KP. Artifacts in Computed Tomography Scanning of Moving Objects. *Seminars in Radiation Oncology* 2004;14:26:19. [PubMed: 14752730]
42. Van Herk M. Errors and Margins in Radiotherapy. *Seminars in Radiation Oncology* 2004;14:52–64. [PubMed: 14752733]
43. Mageras GS, Yorke E. Deep Inspiration Breath Hold and Respiratory Gating Strategies for Reducing Organ Motion in Radiation Treatment. *Seminars in Radiation Oncology* 2004;14:65–75. [PubMed: 14752734]

44. Sharp GS, Jiang SB, Shimizu S, et al. Prediction of respiratory tumour motion for real-time image-guided radiotherapy. *Physics in Medicine and Biology* 2004;49:425–440. [PubMed: 15012011]

Figure 1.

Image fusion of the kV simulation CT scan and MV CBCT scan for patient 1 in axial, sagittal, and coronal views. The “CT GTV” is outlined in green, and the “MV GTV” in white.

Figure 2.

(A) The variation in GTV volume: CT GTV volume (scan 0) and MV GTV volumes (scans 1-5). The mean percent change in MV GTV volume relative to CT GTV is given in the column "Chg" in the legend. Patients 1-4 are non-gated; 5-8 are gated. (B) The slope (shaded bar) of the linear regression analysis for the MV CBCT volume over the treatment course, presented as daily percent change relative to the first scan volume. Error bars are the 95% confidence interval for testing whether the slope is statistically significantly different from zero.

Figure 3.

Mean GTV centroid displacement (light shaded bar for non-gated patients, dark shade for gated patients) for the eight patients (2 lesions in Patient 1) in (A) right-left (RL), (B) anterior-posterior (AP), (C) superior-inferior (SI) directions. Error bars are the 95% confidence interval (Eq. 2) to test whether the mean displacement is statistically significantly different from 0. Negative displacement in RL, AP, or SI direction denotes that the mean MV GTV centroid is to the right, anterior, or inferior of the CT GTV centroid. (D) is the mean 3D displacement $(RL^2 + AP^2 + SI^2)^{1/2}$ for each patient, with error bars indicating plus/minus one standard deviation.

(A)

(B)

(C)

(D)

Figure 4.

Mean setup error (light shaded bars for non-gated patients, dark for gated patients) for the eight patients in (A) RL, (B) AP (C) SI directions. Error bars are the 95% confidence interval (Eq. 2) to test whether the mean setup error is statically significantly different from 0. RL, AP, or SI>0 means anatomy on port film must shift left, posterior, or superior to match DRR. (D) is the mean (shaded bars) and one standard deviation (error bars) GTV centroid displacement and setup error in each direction, averaged over the eight patients.

Figure 5.

Directional analysis plots of (a) mean and (b) worst (closest) MV GTV-to-GTV10 distance (in cm) from 4 MV CBCT scans of patient #4 (non-gated). Negative values (colors orange, yellow, green, blue) indicate that MV GTV is within the GTV10 volume, while dark red region indicates directions where MV GTV protrudes outside the GTV10 volume. Axial sections of (c) planning CT and (d) MV CBCT scan 4 (corresponding to largest MV GTV displacement), showing CT GTV contours in red and MV GTV in blue. Sagittal sections of MV CBCT scans 1 through 4 are shown in (e) through (h), respectively. MV scan 4 (h) shows the largest deviation of the MV GTV occurring anteriorly and inferiorly.

Figure 6.

Directional analysis plots of (a) mean and (b) worst (closest) MV GTV-to-GTV10 distance (in cm) from 5 MV CBCT scans of patient #8 (gated). Axial section of composite planning CT/MV CBCT image for (c) MV CBCT scan 1 and (d) scan 5, showing CT GTV contours in red and MV GTV in blue. Sagittal section MV CBCT of (e) scan 1 and (f) scan 5. In scan 1 the MV GTV is displaced anteriorly and superiorly, while in scan 5 it is displaced left, anteriorly, and inferiorly.

Demographics of the eight MV CBCT patients. Nine lesions (two from Patient #1) were studied. All cases were treated with 6 MV photons, 2 Gy per fraction using multiple IMRT co-planar beams. Abbreviations: a = adenocarcinoma; s = squamous cell carcinoma; nos = non-small-cell carcinoma; rt = right; lt = left.

Table 1

ID	Dose (Gy)	Histology	Location	Stage	Treatment technique	# beams
1a	70	a	Rt lateral upper lobe	T1	Non-gated	3
1b	70	a	Lt lower lobe	T1	Non-gated	3
2	60	s	Rt mediastinum	Recurrent	Non-gated	3
3	70	nos	Lt lateral upper lung	IIIB	Non-gated	7
4	64	s	Lt lower lobe	T1	Non-gated	4
5	80	a	Top of lt lower lobe	IA	Gated	3
6	40	a	Lt hilum	Recurrent	Gated	5
7	80	a	Lt upper lobe	T2N0	Gated	4
8	66	a	Lt lower lobe	IIIA	Gated	5