Predictive Factors for Lung Dose Reduction by Respiratory Gating at Radiotherapy for Lung Cancer

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Lung cancer/Gated radiotherapy/Lung dose/Patient selection/4D-CT.

This study aimed to identify factors predictive of the benefit of respiratory-gated radiotherapy. Three plans were created for 25 patients with non-small cell lung cancer, simulating the following 3 treatment scenarios. Protocol 1 was non-gated and the lung dose was calculated using 4-s slow CT (PnA), protocol 2 was also non-gated and the lung dose was calculated by CT at the end-expiration phase (PnE), and protocol 3 applied phase-based gating around end-expiration (PgE). We correlated possible predictive factors with the estimated lung dose reduction achieved by respiratory gating. The 3D clinical target volume (CTV) motion, craniocaudal CTV motion, and the craniocaudal CTV position were correlated with the reduction in V20 and the mean lung dose ($p < 0.01$). CTV was not significantly correlated with the estimated lung dose reduction. The area under the ROC curve (AUC) for 3D- and craniocaudal CTV motion, and craniocaudal CTV position was 1.000, 0.997, and 0.943, respectively, when the threshold for selecting patients was set at a 1% reduction of V20 and at a 0.5 Gy reduction in the mean lung dose. The results of the present study suggest that 3D CTV motion, craniocaudal CTV motion, and the craniocaudal CTV position are useful for predicting the benefit of respiratory-gated radiotherapy in lung cancer patients.

INTRODUCTION

Respiratory motion may significantly affect the accuracy of tumor targeting with radiotherapy.1,2) Respiratory gating is a technique used to mitigate the effects of respiratory motion during radiotherapy (RT) for lung cancer.3–6) Due to the intermittent delivery of radiation during gated RT, tumor motion within the gating window is limited. As gated RT minimizes the volume of lung parenchyma receiving irradiation, radiation-induced pulmonary toxicity can be reduced without compromising tumor control, especially in three-dimensional (3D) conformal RT with large fraction size. However, gated RT has several disadvantages; treatment planning- and daily patient set-up procedures are complicated and laborious and the time required for RT is increased because irradiation is delivered only at selected phases of the respiratory cycle. Therefore, criteria for identifying patients who may derive significant benefits from respiratory gating must be established.

The dosimetric benefits of respiratory gating increased with tumor mobility.7–9) Underberg et al.7) who analyzed four-dimensional computed tomography (4D-CT) data sets of stage I lung cancer patients reported a correlation between the magnitude of 3D tumor mobility vector and the reduction in the planning target volume (PTV). They suggested a threshold of at least a 50% PTV reduction as a potential indication for gated stereotactic RT. In 20 patients Starkschall et al.9) studied CT data sets obtained with assisted breath holding at 100% and 0% tidal volume. They found that there was a significant decrease in lung dosimetric parameters by respiratory gating with an increase in tumor excursion, especially with GTV less than 100 cm³. Based on these observations, 3D tumor motion may be the most accurate predictor of the lung dose reduction facilitated by respiratory gating. However, to evaluate 3D tumor motion, complex and laborious procedures, including 4D-CT scanning or breath hold techniques are required. Therefore, more easily assessable alternative factors for 3D tumor motion must be identified.

We performed this study in efforts to detect factors predictive of a reduction in lung dosimetric parameters and to identify patients likely to benefit from respiratory gating, assuming 3D conformal radiotherapy with medium to large fraction size. We also attempted to develop criteria for the selection of patients who would manifest a preset degree of dose reduction by respiratory gating.
MATERIALS AND METHODS

Patients

Between January 2007 and February 2009, 36 consecutive patients with non-small cell lung cancer underwent 4D-CT scanning to optimize the radiation field based on respiratory motion. Of these, 25 patients with 25 tumors manifested respiratory regular enough for the acquisition of 4D CT images of acceptable quality, and the CT data sets of the 25 patients were used to simulate different treatment scenarios.

The patients ranged in age from 38 to 90 years (median age, 73 years). Seventeen patients were male and 8 patients were female. The numbers of patients at each clinical stage were as follows: stage I, 7; stage II, 5; stage III, 11; stage IV, 2. Among the 25 tumors, 11 were located in the right lung (3 in the right upper-, 1 in the right middle-, and 7 in the right lower lobe); of the 14 others, 10 were in the left upper- and 4 in the left lower lobe. The average (± S.D.) clinical target volume (CTV) delineated on CT data set 6 (CT-6, CT data sets corresponding with end-expiration) was 65.2 cm³ (± 59.6 cm³). The average (± S.D.) 3D- and craniocaudal CTV motion was 4.2 mm (± 4.8 mm) and 3.6 mm (± 4.9 mm), respectively. The average craniocaudal CTV position relative to the carina was –0.9 cm (range, –10.0 to 7.3 cm). The craniocaudal position was expressed as a positive number when the CTV centroid was above-and as a negative number when it was below the carina.

CT data acquisition

All patients underwent 2 successive CT scans within 30 min for treatment planning, 4D-CT, and 4-s slow CT. For all data acquisitions we used a GE LightSpeed RT (GE Medical Systems, Waukesha, WI) scanner. We reported the procedure for 4D- and 4-s slow CT scanning elsewhere. Briefly, for 4D-CT, the scanner was operated in axial cine mode; the cine interval covered at least the duration of one respiratory cycle plus time for one gantry rotation. A commercial external respiratory monitor system (Real-Time Position Management system, Varian Medical Systems, Palo Alto, CA) was used to record respiratory motion in its temporal correlation with CT scan acquisition; analysis of all reconstructed images was with a commercial image sorting software package (advantage 4D, GE Medical Systems, Waukesha, WI). Ten 3D-CT image sets (CT1-CT10) were obtained from one 4D-CT data set. CT-6 and CT-1 corresponded to the 3D-CT image sets at end-expiration and end-inspiration, respectively. At 4-s slow CT scanning, the images were acquired with a gantry rotation time of 4 sec per slice to approximate the time average of the 4D data sets.

Target delineation and treatment planning

The same radiation oncologist contoured the CTV and defined 10 CTVs (CTV 1-10) at different respiratory phases on 10 corresponding 3D-CT image sets (CT 1-10). The CTVs were contoured to include the gross tumor volume and microscopic tumor extension, using a standardized window setting (level = –500, width = 1500). The composite CTVs were considered the internal target volumes (ITVs) for the different protocols. We added a 5-mm set-up margin to the ITVs to generate the PTVs. Isotropic 5-mm margins beyond the PTV were added to render the dose distribution within the PTV more homogeneous. Based on a radiation dose of 60 Gy, we used 4–8 individually optimized static 6-MV X-ray beams. The dose was prescribed at the isocenter. Inhomogeneity corrections based on the superposition method were employed. The ipsilateral and contralateral lungs were contoured with the algorithm of the 4D simulation software. Total lung volumes were determined using a commercially available treatment planning system (XIO, Computerized Medical Systems, St. Louis, MO).

We assumed phase-based gating around end-expiration and defined a length of 30% of a full respiratory cycle as a gating window. For each patient we developed 3 protocols to simulate different treatment scenarios: 2 protocols for simulating non-gated treatment (PnA, PnE) and one for simulating gated RT around end-expiration (PgE). Under PnA and PnE, all 10 CTVs (CTV 1-10) were combined to form a composite CTV; the dose distribution was calculated on 4-s slow CT scans (PnA) and on CT-6 that corresponded to the 3D-CT image set at end-expiration (PnE). Under PgE, 3 CTVs around end-expiration (CTV 5-7) were combined to form a composite CTV using CT-6 for dose calculations. Figure 1 summarizes these 3 treatment protocols. In each patient we used identical treatment parameters for each of the 3 protocols including the location of the isocenter, the beam directions, and beam weighting. To evaluate the protocols we used 2 dosimetric parameters, i.e. the mean lung dose (MLD) and V20 (% of total lung receiving ≥20 Gy). We did not subtract target volumes from lung volumes. We calculated differences in the lung dosimetric parameters between PnA and PgE, and between PnE and PgE to estimate the dose reduction obtained by respiratory gating.

Candidate factors to predict the dose reduction achieved by respiratory gating

We evaluated 4 factors as possible predictors for the lung dose reduction achievable by respiratory gating: (1) 3D CTV motion, (2) craniocaudal CTV motion, (3) the craniocaudal position of the CTV centroid relative to the carina on CT-1 (CT data set corresponding to end-inspiration) and (4) the CTV on CT-6 (CT data set corresponding to end-expiration). 3D- and craniocaudal CTV motion were defined as the 3D- and craniocaudal distance from the end-inspiration CTV centroid to the end-expiration CTV centroid, respectively. The position of the CTV centroid and the volume enclosed within the CTV contour was calculated by a commercially available treatment planning system. The relationship
between the estimated dose reduction by respiratory gating and these 4 factors was analyzed.

**Statistical analysis**

To compare lung dosimetric parameters among the different protocols, we used the Tukey test. Possible associations between the estimated dose reduction by respiratory gating and the 4 candidate factors were tested with Pearson’s correlation coefficient. Receiver-operating characteristics (ROC) curve analysis was used to assess the predictive value of the candidate factors. All statistical tests were performed with commercial spreadsheet software (Microsoft Office Excel 2007, Microsoft Corp., Redmond, WA). A value of \( p < 0.05 \) was considered statistically significant.

**RESULTS**

**CTVs and lung volumes**

Figure 2 shows the CTVs determined with the 3 protocols and the total lung volumes estimated on 2 different CT image sets, i.e. 4-s slow CT, and CT-6 representing end-expiration. In all 25 patients CTV was larger under the non-gated- (PnA and PnE) than the gated protocol (PgE). The average CTV was 84.7 cm\(^3\) for PnA and PnE, and 71.8 cm\(^3\) for PgE.

In all patients, the lung volume estimated on 4-s slow CT scans was larger than on CT-6. The average lung volume was 3110 cm\(^3\) on 4-s slow CT, and 2972 cm\(^3\) on CT-6, indicating that the ratio of the average lung volume during a respiratory cycle to the end-expiration lung volume was approximately 105:100 under free-breathing conditions.

**Target volume coverage and lung dosimetric parameters**

In the same patient, PTV coverage was similar under all 3 protocols. The percent of PTV receiving at least 95% of the prescribed dose (V95) and the dose received by at least 95% of the PTV (D95) were calculated for each protocol. For all patients, the difference in V95 among the 3 protocols was 0.2% on average (range 0.0–6.7%); the difference in D95 was 0.1 Gy on average (range 0.0–1.3 Gy).

As shown in Fig. 3, MLD under the PnA-, PnE-, and PgE protocol was 6.5 Gy, 6.6 Gy, and 6.1 Gy on average, respectively; V20 was 12.8%, 13.0%, and 12.1% on average. PgE delivered the lowest doses. The lung dosimetric parameters were significantly reduced by respiratory gating, irrespective of whether 4-s slow CT scan or CT-6 was used for dose calculation in the non-gated protocol. Although PnE tended to deliver slightly higher doses than PnA, the difference was not statistically significant. In the following analysis we used PnA as the non-gated treatment protocol and considered the difference in lung dosimetric parameters between PnA and PgE as an estimate of the dose reduction achieved by respiratory gating.

**Candidate factors to predict dose reduction by respiratory gating**

We analyzed the relationship between 3D CTV motion and the other 3 factors. There was a strong correlation between 3D CTV motion and craniocaudal CTV motion (Pearson correlation coefficient 0.990, \( p < 0.01 \)) and a significant correlation between 3D CTV motion and the craniocaudal CTV position relative to the carina (Pearson correlation coefficient –0.803, \( p < 0.01 \)). Tumors located caudally tended to show larger motion. Between 3D CTV motion and CTV there was no statistically significant correlation (Pearson correlation coefficient 0.070, \( p = 0.74 \)).

**Correlation between predictive factors and estimated lung dose reduction by respiratory gating**

The difference in lung dosimetric parameters between PnA and PgE was considered as the estimated dose reduc-
Fig. 2. CTV and lung volume of the 25 lung cancer patients.

Fig. 3. Mean lung dose and V20 (percentage of total lung receiving ≥20 Gy) of the 3 protocols in 25 patients. Mean lung dose under the PnA-, PnE-, and PgE protocol was 6.5 Gy, 6.6 Gy, and 6.1 Gy on average, respectively; V20 was 12.8%, 13.0%, and 12.1% on average.
Selection of Patients for Gated Radiotherapy

The selection of patients for gated radiotherapy. The relationship between the estimated lung dose reduction and the 4 predictive factors is shown in Fig. 4. There was a significant positive correlation between the reduction in the lung dosimetric parameters and 3D- and craniocaudal CTV motion. There also was a significant correlation between the reduction in the lung dosimetric parameters and the craniocaudal CTV position relative to the carina. The achieved dose reduction tended to be greater in tumors located caudally than cranially. There was no statistically significant correlation between the reduction in the lung dosimetric parameters and the CTV.

**ROC analysis of the predictive factors**

ROC analysis to test the predictive capacity of 3D CTV motion, craniocaudal CTV motion, and the craniocaudal CTV position relative to the carina showed a significant correlation with the estimated lung dose reduction by respiratory gating.

We set the threshold for selecting patients for respiratory gating at a 1% reduction in V20 and at a reduction of 0.5 Gy in the mean lung dose. By this threshold 10 of the 25 patients (40%) would be selected for gated radiotherapy. Figure 5 shows the ROC curves for detecting patients who may be expected to allow a greater reduction in the dosimetric parameters than the determined threshold. The area under the ROC curve (AUC) for 3D CTV motion, craniocaudal CTV motion, and craniocaudal CTV position relative to the carina was 1.000 (cut-off = 0.5 cm, sensitivity = 100%, specificity = 100%), 0.997 (cut-off = 0.4 cm, sensitivity = 100%, specificity = 93%), and 0.943 (cut-off = 3 cm below the level of the carina, sensitivity = 90%, specificity = 87%), respectively.

We then set two additional thresholds at a reduction of 0.7 Gy and 0.2 Gy in the mean lung dose. When we set the threshold at a reduction of 0.7 Gy in the mean lung dose, 5 of the 25 patients (20%) would be selected for respiratory

![Fig. 4](image1.png)

**Fig. 4.** Correlation between the 4 predictive factors and the estimated lung dose reduction achieved by respiratory gating. Upper: mean lung dose, lower: V20.

![Fig. 5](image2.png)

**Fig. 5.** Receiver-operating characteristics (ROC) curves for detecting patients with a reduction of more than 1% of V20 (percentage of total lung receiving ≥20 Gy) and a reduction of more than 0.5 Gy of the mean lung dose by respiratory gating.
gating, and the AUC for 3D CTV motion, craniocaudal CTV motion, and craniocaudal CTV position was 0.875, 0.855 and 0.755, respectively. When we set the threshold at a reduction of 0.2 Gy in the mean lung dose, 14 of the 25 patients (56%) would be selected for respiratory gating, and the AUC for 3D CTV motion, craniocaudal CTV motion, and craniocaudal CTV position was 0.922, 0.916 and 0.903, respectively. At each threshold, i.e. 0.2 Gy, 0.5 Gy or 0.7 Gy reduction in the mean lung dose, the AUC for craniocaudal CTV motion was consistently slightly smaller than for 3D CTV motion and larger than for craniocaudal CTV position, suggesting that the predictive value of these factors to select patients did not depend on the threshold setting.

DISCUSSION

As the extent of 3D tumor motion has been shown to be associated with the lung dose reduction by respiratory gating, we posited that it represented the best predictor of the lung dose reduction by respiratory gating. However, to measure 3D tumor motion, considerably complex and laborious procedures such as 4D-CT scanning, not available in all institutions, or breath hold techniques are required. Therefore, the identification of alternative factors indicative of 3D tumor motion, by for example chest X-p or routine CT, may facilitate the selection of patients who may benefit from respiratory gating. In fact, craniocaudal CTV motion can be evaluated by fluoroscopy, the craniocaudal CTV position relative to the carina by chest X-p or routine CT, and CTV by routine CT.

Throughout our study we used the phase mode of the RPM system to fix the gating window to cover a 30% duty cycle around end-expiration. In an earlier investigation, we compared the lung dosimetric parameters and treatment times between gating around end-expiration and end-inspiration. We found that when we used phase-based gating they were similar, irrespective of whether gating was around end-expiration or end-inspiration. Another issue to be considered is the possible intra- and interfractional reproducibility of the tumor position, since during 4D-CT scanning, respiratory tumor motion is captured based on only a few respiratory cycles. Although the reproducibility of the tumor position has not been fully investigated, under free-breathing conditions it appears to be more stable around end-expiration than end-inspiration. Therefore, in the present study, we chose gated treatment around end-expiration. Balancing the prolongation of treatment time against the reduction in lung dosimetric parameters, we determined the width of the gating window to be a 30% duty cycle.

In our dosimetric analysis we did not employ the most current 4D dose calculation techniques, rather, we used a 3D dose calculation technique. This made it necessary to choose a CT data set for calculating the dose distribution. Underberg et al. compared the lung dosimetric parameters between non-gated and gated plan using the end-expiratory CT set for dose calculation in both plans. Starkshall et al. also estimated the dosimetric benefit of respiratory gating using the same CT set in both non-gated and gated treatment plans. When the same CT is used for dose calculation in the non-gated and gated plan, the dosimetric gain of respiratory gating might not be correctly estimated because the difference in lung status is not taken in consideration. More accurately, one could use the free-breathing data set in the non-gated plan and the end-expiration data set in the plan simulating gated irradiation around end-expiration, although this method is more time-consuming. We developed 2 protocols for non-gated irradiation using 2 different CT sets: 4-s slow CT (PtA), and CT-6 that corresponded to the 3D-CT image set at end-expiration (PtE). There was no statistically significant difference in the lung dosimetric parameters between these 2 protocols. It seemed acceptable to use the data set corresponding to end-expiration for simulating both non-gated and gated treatment, at least for the purpose of estimating the benefit of respiratory gating.

We demonstrated that the estimated reduction in the lung dose was significantly correlated with 3D CTV motion, craniocaudal CTV motion, and also the craniocaudal position of CTV. Based on our ROC curve analysis, we considered 3D CTV motion to be the best predictor among the 3 factors we investigated. Craniocaudal CTV was slightly less predictive than 3D motion; however, the difference between it and 3D motion was negligible. Although the craniocaudal CTV position relative to the carina was a useful predictive factor, it was less useful than 3D and craniocaudal CTV motion.

With its direction, i.e. medial-lateral, anterior-posterior, and cranial-caudal, the magnitude of lung tumor motion differs; it was greatest in the craniocaudal direction, particularly with respect to tumors in the lower lobe. We also found a strong correlation between 3D CTV motion and craniocaudal CTV motion, and our ROC curve analysis showed that 3D- and craniocaudal motion were similarly predictive of the lung dose reduction. The high predictive value of craniocaudal motion may partly be explained by the limited use of non-coplanar beams in thoracic RT. Because the craniocaudal component is small relative to the total beam direction, the lung dose is more sensitive to the degree of cranial-caudal- than medial-lateral- or anterior-posterior motion.

Lung tumors located caudally tended to show larger motion. Liu et al. who assessed the 3D motion of 166 lung tumors using 4D-CT data sets reported that tumor motion was associated with the cranial-caudal tumor position; the degree of motion was not associated with their medial-lateral or anterior-posterior position. We found that the cranial-caudal CTV position was a fairly useful predictive factor for the lung dose reduction by respiratory gating and we posit a correlation with tumor motion. In the ROC curve
analysis, its predictive value was lower compared with 3D- or craniocaudal CTV motion. Nonetheless, considering that the craniocaudal tumor position can be assessed on chest X-p films, it does have value as a useful predictor.

The movement of small- tends to be greater than of larger tumors although the correlation between tumor size and motion seems to be relatively weak.\textsuperscript{3,20} We found no statistically significant correlation between the CTV and the estimated reduction in the lung dosimetric parameters, suggesting that the tumor size is not a useful predictive factor for selecting patients eligible for respiratory gating.

In our study we assumed the use of a medium to large fraction size in 3D conformal RT for lung cancer. At present, little is known concerning the relationship between the radiation dose and lung toxicity and no clear relationship was found between lung dosimetric parameters and lung toxicity at RT with large fraction size.\textsuperscript{24,25} Borst \textit{et al.}\textsuperscript{26} who analyzed 128 lung cancer patients treated with stereotactic RT using a wide variety of doses and fractionations suggested a dose-response relationship between the risk of radiation pneumonitis and MLD in patients undergoing stereotactic as well as conventionally fractionated RT. They reported a significant dose-response relationship in radiation pneumonitis after stereotactic RT when MLD was converted to the 2 Gy-equivalent dose using the $\alpha/\beta$ ratio of 3 Gy. It remains unclear how clinical toxicity can be best estimated from lung dosimetric parameters, particularly when a large fraction size is involved. The dose-response relationship observed at conventionally fractionated RT\textsuperscript{27,28} cannot be simply extrapolated. Furthermore, when a hypofractionated schedule with a fraction size over 10 Gy is used, the classical linear-quadratic model may not be appropriate to convert the given dose into the equivalent dose delivered at smaller fraction sizes.

Assuming the use of a large fraction size, the patient-averaged V\textsubscript{20} of 12.8% and MLD of 6.5 Gy in our PhA protocol may not be appropriate considering the relatively small $\alpha/\beta$ ratio of the lung. The clinical significance of a 1% reduction in V\textsubscript{20} and a 0.5 Gy reduction in MLD, the threshold we applied for the selection of patients for respiratory gating, must not be underestimated. We set several thresholds to select patients for respiratory gating, and the candidate factors showed a consistent tendency in the predictive value. Although the absolute threshold for selecting patients for gating must take into account patient characteristics and treatment protocols, the relative predictive value of the factors for lung dose reduction identified in the present study may be useful for establishing patient selection criteria for gated RT irrespective of the treatment protocol. In our study we assumed RT with medium to large fraction size, and included the patients with tumors of various volumes. The relatively heterogeneous patient population may be a limitation of the present study. However, the consistent results in the ROC analysis using different threshold values suggest that the results of the present study could be applicable to patients with tumors with various sizes.

In conclusion, our evaluation of 4 factors for predicting the lung dose reduction obtained by respiratory gating revealed that 3D CTV motion was the best predictor. Although craniocaudal CTV was slightly less predictive than 3D motion, the difference was negligible, making it a useful alternative predictor for 3D motion. The craniocaudal position of CTV relative to the carina was less predictive than 3D- or craniocaudal CTV motion. We found that CTV was of no predictive value.

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