Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2010 August 1; 77(5): 1553–1560. doi:10.1016/j.ijrobp.2009.12.064.

Inferring Positions of Tumor and Nodes in Stage III Lung Cancer from Multiple Anatomical Surrogates Using 4D CT

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Abstract

Purpose—To investigate the feasibility of modeling Stage III lung cancer tumor and node positions from anatomical surrogates.

Method—To localize their centroids, the primary tumor and lymph nodes from 16 Stage III lung cancer patients were contoured in 10 equal-phase planning 4D CT image sets. The centroids of anatomical respiratory surrogates (carina, xyphoid, nipples, mid-sternum) in each image set were also localized. The correlations between target and surrogate positions were determined, and Ordinary-Least-Squares (OLS) and Partial-Least-Squares (PLS) regression models based on a subset (3–8 randomly selected) of respiratory phases were created to predict the target positions in the remaining images. The 3-phase image sets that provided the best predictive information were used to create models based on either the carina alone or all surrogates.

Results—The surrogate most-correlated to target motion varied widely. Depending on the number of phases used to build the models, mean OLS and PLS errors were 1.0–1.4mm and 0.8–1.0mm, respectively. Models trained on the 0%, 40%, and 80% respiration phases had mean(±standard deviation) PLS errors of 0.8±0.5mm and 1.1±1.1mm for models based on all surrogates and carina alone, respectively. For target coordinates with motion>5mm, mean 3-phase PLS error based on all surrogates was 1.1mm.

Conclusion—Our results establish the feasibility of inferring primary tumor and nodal motion from anatomical surrogates in 4D CT scans of Stage III lung cancer. Using inferential modeling to decrease the processing time of 4D CT scans may facilitate incorporation of patient-specific treatment margins.

Keywords

intra-fraction motion; 4D CT; respiratory surrogates; nodal volume; carina

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Conflict of Interest: None

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I. Introduction

In the absence of motion management techniques, respiration-induced tumor motion reduces the accuracy and effectiveness of radiation therapy.^{1–4} 4D CT has emerged as a standard tool for respiratory motion assessment.^{5–7} Recently, a number of groups have recommended the use of 4D CT to assess patient-specific nodal volume motion in Stage III lung cancer.^{8–11} They caution against the possibilities of large-magnitude motion,⁸ inter-patient motion variability,^{9–12} and differences in the motion of individual nodal volumes compared to the primary tumor and other nodes.^{9–11}

The time-consuming nature of manually contouring relevant structures in each of the volumetric datasets in a 4D CT precludes its routine use in many clinics. As an alternative, 4D CT post-processing techniques such as maximum intensity projection (MIP) analysis and combining the contoured GTV at end-inspiration with the contoured GTV at end-expiration have been developed to improve treatment planning efficiency.² However, while the space between cancerous tissue and adjacent structures in advanced stage lung cancer is usually visible in 3D CT and 4D CT scans, the target boundaries become blurred in MIPs if the mediastinum, chest wall, diaphragm, or vasculature occupy the same space as the target during different respiratory phase bin images.^{13–15} Ezhil *et al.* observed this phenomenon in both primary tumors and nodal volumes,¹⁴ and both Rietzel *et al.* and Ezhil emphasized the importance of validating MIP-defined target volumes by visually comparing them to each respiratory phase image of the 4D CT and contouring additional respiratory phase images if necessary.^{14–15} Thus, this “MIP-Modified” method, while faster than contouring each volumetric image, does require assessing the target volumes in each 4D CT volumetric image.

In this study, we propose a new approach (Figure 1) for decreasing the contouring burden of 4D treatment planning for Stage III lung cancer, whereby (1) the target volumes (including the primary tumor and nodes) in a *subset* of respiratory phase bin images are localized, (2) a group of anatomical respiratory surrogates in *all* image sets corresponding to respiratory phase bins are localized, (3) a mathematical model relating target position to anatomical surrogate positions is created, and (4) target positions in the *uncontoured* images are determined using the model.

Previously studied respiratory surrogates such as the chest wall,¹⁶ diaphragm,^{17–19} and carina^{19–20} as well as external respiratory surrogates such as abdomen and chest surface motion^{4,17,21–27} and lung volume.^{4,21} Since there are often significant differences between respiratory surrogate signals and tumor motion, and because the tumor position varies for particular external surrogate positions,^{16,22–25} incorporating multiple markers into a model of tumor motion has been recommended to improve the accuracy of respiratory surrogate systems.^{28–32} Possible approaches for inferring tumor position from surrogates include linear²⁸ and Partial-Least-Squares²⁹ regression, smoothing splines,³⁰ moving averages,³³ and higher order polynomials.³⁴

We first characterized the relationship between primary tumors and nodal volumes with a series of anatomical surrogates visible in 4D CT images: carina, xiphoid, nipples, and mid-sternum. We then applied two mathematical modeling techniques, Ordinary-Least-Squares (OLS) and Partial-Least-Squares (PLS), for inferring tumor and nodal volume positions from the surrogates. To examine the limits of this method, we tested models based on as few as 3 contoured respiratory phases, and we compared models based on all available surrogates to models based on carina position alone.

II. Methods and Materials

A. 4D CT Position Data

The VU University Medical Center database of planning scans was evaluated retrospectively to identify patient scans with both clearly demarcated mediastinal lymph nodes and the absence of 4D imaging artifacts. Patients were scanned in the supine position on a 16-slice CT scanner (LightSpeed 16; GE Healthcare; Waukesha, WI) with no intravenous contrast. Scans were performed in cine acquisition mode at 2.0 cm intervals, and images had a slice thickness of 2.5 mm. Patients were instructed to breathe normally with a regular rhythm. The respiratory signal was detected using the Real-time Position Monitoring (RPM) system (Varian Medical Systems, Palo Alto, CA). Images were obtained only after a quiet, regular breathing pattern was observed. All images and corresponding respiratory signal files were binned into 10 separate respiratory phases of equal time intervals. The phases were labeled from 0% to 90%, with end-inspiration corresponding to the 0% bin.

A single radiation oncologist (JRP) manually contoured the primary tumors and the nodal volumes and localized the anatomical respiratory surrogates, and a second radiation oncologist verified the contours. We included both benign and malignant nodes, regardless of size, and classified them according to the 1997 Mountain and Dresler system (Table 1).³⁵

The anatomical surrogates were xyphoid (n=16), carina (n=16), left (n=7) and right (n=11) nipples (tracked in male patients only), and mid-sternum (n=15). We localized the mid-sternum by identifying a metal marker placed at the time of 4D CT, and we localized the carina by identifying the peak between main-stem bronchi on coronal image slices, which had been automatically interpolated by the treatment software.

Depending on their visibility in the 4D CT scan, 3–5 anatomical surrogates were tracked for each patient. In total, 3D position data from 16 primary tumors, 53 nodal volumes, and 65 anatomical surrogates from the 16 patients were analyzed. Subsequently, the centroid of the contoured volumes was used to describe their displacements.

B. Nodal Volume- and Tumor-Surrogate Correlation

We measured the correlations between positions of each primary tumor/nodal volume and positions of each anatomical surrogate in three orthogonal directions: medial-lateral (ML), anterior-posterior (AP), and superior-inferior (SI).

C. Modeling Tumor and Nodal Volume Position Using Anatomical Surrogates

C.1. Modeling Methods—We used two methods, Ordinary-Least-Squares (OLS) and Partial-Least-Squares (PLS), to model the position of the primary tumor or a node as a function of anatomical surrogate positions. Both OLS and PLS operate according to $\hat{Y} = X \cdot B$, where X is an $m \times n$ matrix of anatomical surrogate coordinates with m measurements (phases) and n variables (position coordinates), B is an $n \times 3$ matrix of regression coefficients, and $\hat{Y}$ is a matrix of $m \times 3$ target position coordinates.

The OLS method defines B as the set of regression coefficients that result in the smallest

possible sum of squared errors, $\sum_i (\hat{Y}_{i,j} - Y_{i,j})^2$, for target position coordinate j and respiratory phases i and approximate and actual target positions $\hat{Y}$ and Y , respectively. The unique OLS solution is given by $B = X^+ \cdot Y$, where X^+ is the Moore-Penrose pseudo-inverse of X . For full-rank, real X , the Moore-Penrose pseudo-inverse is defined as $X^+ = X^T (X^T \cdot X)^{-1} \cdot X$. For rank-deficient, real X , $X^+ = V \cdot \Sigma^+ \cdot U^T$, where U , Σ , and V are the matrices in the

singular value decomposition of X given by $X = U \cdot \Sigma \cdot V$. The terms of Σ^+ are given by

$$\Sigma_{i,j}^+ = (\Sigma_{i,j})^{-1} \text{ for } \Sigma_{i,j} \neq 0 \text{ and } \Sigma_{i,j}^+ = 0 \text{ for } \Sigma_{i,j} = 0.$$

PLS regression is a second technique for determining the coefficient matrix, B , in $\hat{Y} = X \cdot B$. PLS compresses the input data matrix, X , into an $m \times A$ matrix of scores (or *latent variables*), $T = [t_1, t_2, \dots, t_A]$. t_i are orthogonal and are linear combinations of the columns of X . We determined the optimal quantity of latent variables, A , for each dataset using cross-validation, in which we repeatedly created models based on various A , each time leaving one sample out and then applying the model to that sample to evaluate the model. We chose the smallest quantity of latent variables that reduced the root-mean-square error in the cross validation set by less than 2% over one fewer latent variables. We then used the SIMPLS algorithm³⁶ to derive the PLS regression coefficients, described below.

The SIMPLS algorithm involves sequentially determining the A scores, weights, and loadings associated with X and Y . The latent variables of Y , u_i for $i = 1$ to A , are linear combinations of the columns of Y that are chosen so as to maximize the covariance between t_i and u_i . The first X score, t_1 , is given by $t_1 = X \cdot X^T \cdot Y_0 / \text{norm}(X \cdot X^T \cdot Y)$, where Y_0 is mean-centered Y . The first X weight, r_1 , and the first X basis, v_1 , are both one. The Y loadings and scores are calculated as $q_i = Y_0^T \cdot t_i$ and $u_i = Y_0 \cdot q_i$, respectively. The X basis is updated with each iteration as $v_i = v_{i-1} - V_{i-1} \cdot (V_{i-1}^T \cdot (t_i^T \cdot X)^T)$, where $V_{i-1} = [v_1, v_2, \dots, v_{i-1}]$. Subsequent X weights and scores are calculated as $r_i = (S_{i-1} - v_i \cdot (v_i^T \cdot S_{i-1})) \cdot q_i$ and $t_i = X \cdot r_i$. The regression coefficient matrix, B , is given by $B = R \cdot Q^T$, where $R = [r_1, r_2, \dots, r_A]$ and $Q = [q_1, q_2, \dots, q_A]$.

C.2. Impact of the Quantity of Contoured Respiratory Phase Images—We attempted to infer primary tumor and node positions from anatomical surrogates using image datasets corresponding to 3–8 randomly chosen respiratory phases. In creating each model, we randomly partitioned the image datasets into *training* and *testing* subsets, where the *training* subset contained 3–8 datasets. We used the *training* subset to create the model and then assessed the accuracy of the results (in the form of target inferred position errors) by applying the model to the *testing* subset. To cross-validate our analysis, we randomly partitioned the dataset 50 times and repeated the analysis for each primary tumor and nodal volume coordinate. Figure 1 summarizes the methodology employed in this work.

C.3. Three-Phase Model Analyses—We next determined the set of three phase bins that, when used to create models, resulted in the lowest overall mean error. To choose this set of phases, we tested models based on each of the 120 combinations of three respiratory phase bins ([0%, 10%, 20%], [0%, 10%, 30%], etc.) for each target, determining separate 3-phase sets for OLS and PLS. Finally, we used the 3-phase sets to create and analyze OLS and PLS models from (1) all available anatomical surrogates and (2) the carina alone.

C.4. Impact of Target Position—To determine whether the 3-phase model error varies with target position, we separated the 53 nodes into (1) upper mediastinal zone (stations 2 and 3), (2) mid-mediastinal zone (stations 4, 5, and 6), and (3) lower mediastinal zone (stations 7 and 8). We did not subdivide the primary tumors by location, because we had insufficient data (N=16).

III. Results

A. Tumor-Surrogate Correlation

The mean ($\pm$ standard deviation) correlations between target position and anatomical surrogate position for nodal volumes and primary tumors were 0.41 ± 0.26 and 0.42 ± 0.26 , respectively. Correlations between target coordinates and anatomical surrogate SI, AP, and ML coordinates (Figure 2) were 0.47 ± 0.27 , 0.42 ± 0.25 , and 0.34 ± 0.24 , respectively.

We determined the anatomical surrogate coordinate that was best correlated with each tumor/node coordinate (see Figure 3). Since some surrogates were not visible in every 4D CT, we normalized the histogram by dividing each anatomical surrogate coordinate count by the number of target coordinates (number of nodal volumes and primary tumors times three orthogonal directions) available for comparison. The carina SI motion was most correlated with both primary tumor and nodal volume motion more often than any other anatomical surrogate coordinate. The mid-sternal AP motion and carina ML motion showed a better correlation with motion of the primary tumor than did the coordinates of other anatomical surrogates, while the nipple AP motion showed a better correlation with motion of the nodes than anatomical surrogate coordinates.

B. Inferring the position of the primary tumor and nodes using anatomical surrogates

We created OLS and PLS models from a randomly chosen subset of 3D datasets corresponding to respiratory phases and using all available surrogates for each patient dataset. While the quantity of latent variables, A , varied for each dataset, most PLS models (100% for 3-phase models decreasing to 65% for 8-phase models) were based on a single latent variable. The models' errors varied with the number of contoured 3D datasets from the 4D CT used to train the models (Figure 4). OLS model error decreased slightly when the number of image sets corresponding to respiratory phases was increased from 3 (mean = 1.1 mm) to 4 (mean = 1.0 mm) but increased monotonically with each additional contoured respiratory phase image set. In contrast, the mean PLS error decreased monotonically from 1.0 mm for 3 phases to 0.8 mm for 8 phases. Errors for nodal volumes were comparable to those of primary tumors. Mean PLS error was significantly less than mean OLS error ($p < 0.05$) for each quantity of training phases.

The average model errors were minimized when the 0%, 40%, and 70% phase bins and the 0%, 40%, and 80% phase bins were used to create the model with OLS and PLS, respectively. In the following analyses, OLS analyses referring to "3-phase" models refer to models trained on data from the datasets corresponding to the 0%, 40%, and 70% respiratory phases; PLS analyses referring to "3-phase" models refer to models trained on data from the datasets corresponding to the 0%, 40%, and 80% respiratory phases.

The overall mean ($\pm$ standard deviation) 3-phase model error for all nodal volumes and primary tumors included in the study and when all anatomical surrogates were used to create the model was 0.8 ± 0.5 mm for OLS and 0.8 ± 0.5 mm for PLS. Model error generally increased with increasing peak-to-peak motion of the target coordinates (Figure 5). The mean ($\pm$ standard deviation) model error for target coordinates whose motion was greater than 5 mm was 1.1 ± 0.6 mm for OLS and 1.1 ± 0.5 mm for PLS. PLS errors for 3-phase models exceeded 2 mm in only 7% of inferred positions (Figure 6).

The mean ($\pm$ standard deviation) 3-phase PLS model error for upper, middle, and lower mediastinal nodes were 0.9 ± 0.6 mm, 0.9 ± 0.7 mm, and 1.1 ± 0.8 mm, respectively. Complete OLS and PLS results are included in Figure 7.

Lastly, we created 3-phase models using 3D carina position data alone. The overall mean ($\pm$ standard deviation) errors for carina-only OLS and PLS models were 2.4 ± 1.1 mm and 1.1 ± 1.1 mm. The carina-only PLS mean ($\pm$ standard deviation) errors for primary tumors and nodal volumes were 1.2 ± 1.4 mm and 1.1 ± 0.9 mm, respectively.

IV. Discussion

To our knowledge, the correlation between lung tumor motion and multiple respiratory surrogates' motion in 4D CT images has not been reported previously. Our results indicate that it is possible to model both primary tumor and nodal volume motion in Stage III lung cancer from anatomical respiratory surrogates. Our main findings were that 1) correlation of tumor motion with a specific respiratory surrogate was patient-specific, 2) carina SI motion was best-correlated with both primary tumor and nodal volume motions more often than any other anatomical surrogate coordinate, and 3) mean modeling error using PLS was on the order of CT resolution

The correlations in our study were lower than the correlations between *abdominal* tumor motion and surrogate motion in 4D CT images reported by Beddar *et al.* and Gierga *et al.*^{23,37} However, both Gierga *et al.* and Ozhasoglu *et al.* observed that surrogate motion and abdominal tumor motion are in phase,^{4,23} whereas the common phase differences between lung tumor and surrogates result in decreased correlation. Gierga suggested that variability in abdominal- and chest-breathing may contribute to a complex relationship between respiratory surrogates and thoracic tissue motion, whereas the relationship between abdominal skin markers and abdominal tumor motion is more direct. This is supported Koch *et al.*, who reported correlations between external respiratory surrogate motion and pulmonary tissue motion that were comparable to the surrogate-target correlations in our study.³⁸

In agreement with Koch *et al.*³⁸ and Yan *et al.*,³⁰ no single respiratory surrogate was consistently better correlated to tumor or nodal volume motion. Rather, the correlation of tumor motion with a specific respiratory surrogate varies by patient. In addition, ML or SI surrogate motion was sometimes better correlated with target motion than AP motion. This implies that external markers tracking only skin AP motion, though common, may not be ideal for all patients.

We did not use the diaphragm as a respiratory surrogate in this study because of the difficulty in localizing the same portion of the diaphragm in images corresponding to the different respiratory phases. The carina is smaller, less deformable, and easier to localize accurately in 4D CT images. The performance of the carina-only models is in agreement with Higgins *et al.*, who found that the carina may be better suited as a registration landmark for inter-fraction patient alignment than the lung tumor itself.³⁹

To date, only a few studies have compared carina positions to tumor or nodal volume positions. Van der Weide *et al.* reported that carina SI motion is well-correlated with total lung volume,²⁰ while Piet *et al.* reported that the distance between the carina and nodal volumes is highly variable. However, Piet *et al.* did not attempt to characterize the relationship between carina motion and nodal volume motion.⁴⁰ We found that the mean error for carina-only PLS models was 1.1 mm, an average of less than 0.5 mm greater than mean error of PLS models incorporating data from all surrogates. The proximity of the carina to locally advanced lung cancer target volumes and its tendency to be in phase with target motion make the carina well-suited to be a surrogate for Stage III primary tumor and nodal volume motion.²⁰

When only 3 phases were used to train the models, the sets of 3 phase bins for which target position prediction was most accurate were the 0%, 40%, and either 70% (for OLS) or 80% (for PLS). The 0% phase bin represents end-inspiration. The phase associated with end-expiration varies by patient due to the gradual change in direction at the end of expiration. Thus, the three phase bins used to train the models include one extreme position (0% phase) and, we speculate, two additional phase bins representing the partial inhalation and partial exhalation data necessary to characterize the path of motion of the target.

The mean 3-phase carina-only PLS model accuracies for primary tumors and nodal volumes differed by only 0.1 mm. Localization accuracy for superiorly positioned mediastinal nodes was slightly better than for inferior nodes. Our conclusion that the model error was positively correlated with peak-to-peak target motion is in agreement with prior studies showing that mediastinal nodes below the carina move more than mediastinal nodes in superior stations.⁸⁻¹⁰

Our results are based on data acquired during normal respiration without coaching aids. We speculate that our models may be improved by using training or audio-visual coaching to induce more regular breathing during 4D CT acquisition. Finally, while our method does not take target volume deformation into account, Liu *et al.* and Wu *et al.* showed that deformable and rotational registration, respectively, results in negligible improvement over rigid tumor registration across 4D CT phases.^{18,41} Thus, our method of combining centroid tracking with target contours determined manually in a single respiratory phase bin image is likely to be sufficient for target delineation in 4D CT.

The modeling methods described in this study may make it possible to localize targets in uncounted images with an accuracy of approximately 1 mm. This technique would require manually identifying anatomical surrogates in only three phases. Comprehensive motion management in Stage III lung cancer, including developing accurate patient-specific treatment margins to account for motion, may be made more accessible, and thus treatment more effective, by reducing the contouring burden of 4D CT through models similar to those tested in this study.

V. Conclusion

In summary, we established the feasibility of inferring the primary tumor and nodal volume motion from anatomical surrogates in 16 4D CT scans of Stage III lung cancer. The results from this work suggest that inferential modeling may have the potential to decrease the time required to process 4D CT scans, thereby improving therapy by allowing for incorporation of patient-specific margins in the planning process.

Acknowledgments

This work was supported in part by a grant from the NIH/NCI CA122403. Research funding for JRP was provided by the Canadian Association of Radiation Oncology in partnership with Elekta Oncology Systems and the University of Ottawa.

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Figure 1. Summary of methodology employed for inferring the positions of the primary tumor and nodal volumes.

Figure 2.
Mean and standard deviations of correlation between anatomical surrogate and tumor for surrogate (a) ML, (b) AP, and (c) SI coordinates. pt = primary tumors, nv = nodal volumes.

Figure 3.

Proportion of primary tumor and nodal volume coordinates that are most highly correlated with each anatomical surrogate coordinate, normalized according to the quantity of data available for that anatomical surrogate.

Figure 4. Means and standard deviations (error bars) of OLS and PLS errors for models trained on a range (3–8) of quantities of contoured volumetric respiratory phase bin images. The standard deviation of the PLS errors is smaller and more consistent than the standard deviation of the OLS errors.

Figure 5.

Target coordinate peak-to-peak motion vs. mean 3-phase PLS model error. Mean error (1.1 mm) for coordinates with peak-to-peak motion > 0.5 cm (points in the gray area) is indicated by the dashed line.

Figure 6. Histogram summarizing inferred position errors of 3-phase PLS models, including all primary tumors and nodal volumes in the dataset. Errors exceeded 0.2 cm in 7% of inferred positions.

Figure 7.
Mean and standard deviation (error bars) of 3-phase model error for nodal volumes, subdivided by the zone of nodal station.

Table 1

Quantity of nodes at each nodal station included in this study.

Nodal station	2R	3A	4R	4L	5	6	7	8
Quantity	6	2	15	10	3	1	15	1