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Assessment of Intra-Fraction Mediastinal and Hilar Lymph Node Movement and Comparison to Lung Tumor Motion Using Four-Dimensional CT

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Abstract

Purpose—To quantify the amount of free-breathing motion measured using 4D CT scans of mediastinal and hilar lymph nodes and to compare this motion to the primary lung tumor motion.

Methods—Twenty patients, with prior 4D CT scans, having primary lung cancer and radiographically positive lymph nodes were retrospectively analyzed. The 4D CT data sets were divided into four respiratory phases and the primary tumor and radiographically positive nodes were contoured. Geometric and volumetric analysis was performed to analyze the motion of the primary tumors and the lymph nodes.

Results—The mean lymph node motion was 2.6 mm in the medio-lateral direction and 2.5 mm in the antero-posterior direction and 5.2 mm in the cranio-caudal direction with a maximum of 14.4 mm. All lymph nodes were found to move inferiorly during inspiration, with 12.5% of nodes moving more than 1 cm. Lymph nodes located below the carina showed significantly more motion than those above the carina ($P = 0.01$). In comparing the primary tumor motion to the lymph node motion, no correlation was identified.

Conclusions—4D CT scans can be used to measure the motion for the primary lung tumor and pathologic lymph nodes encountered during the respiratory cycle. Both the primary lung tumor and the lymph node need to be examined to assess their individual degree of motion. The study demonstrated the need for individualized plans to assess the heterogeneous motion encountered in both primary lung tumors and among lymph node stations.

Keywords

4D CT; lung cancer; mediastinal lymph nodes; radiation therapy

Introduction

Currently, lung cancer is the most common cause of cancer death in both men and women. The American Cancer Society estimates that in 2006, lung cancer will account for more than

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Conflict of Interest Notification

No actual or potential conflicts of interest exist.

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160,000 deaths in the United States.¹ Locally advanced carcinomas, defined as stage III or greater, comprise a significant proportion of these deaths. For these locally advanced lung cancers, radiation therapy is the primary treatment option available. Radiation therapy has undergone a dramatic revolution during the last decade. With the advancement of newer treatment modalities and onboard imaging, radiation oncologists are now able to deliver therapy in a more precise distribution, providing a higher overall dose to the tumor while still limiting radiation to normal tissue. Dose escalation of this kind may improve overall survival without an increase in damage to normal tissue.²

Even with the improved ability to conform the radiation dose, margins are still needed to account for both setup error and organ motion. With lung cancer, respiratory movement can cause a significant amount of tumor motion, especially for tumors within the lower lobes.^{3,4} The tumor motion can lead to inaccuracies in treatment delivery and can potentially lead to under-dosing of the tumor. Typically a margin ranging from 1 to 2 cm has been considered effective in accounting for both the setup error and potential organ motion.^{5,6} However, local failure rates as high as 80% still occur,^{4,7} suggesting that the radiation dose that is prescribed today is insufficient in controlling the disease.

Because tumor motion cannot be predicted clinically using tumor size, tumor location, or pulmonary function tests,^{8,9} it must be assessed on an individual basis for each patient. In order to more accurately predict the extent of tumor motion within individual patients, four-dimensional (4D) computed tomography (CT) has been developed to retrospectively image motion during the respiratory cycle.^{10–13} The 4D CT process can be used to track tumor and lung tissue motion during breathing or to determine the extent of margin needed for treatment planning. The 4D CT images can account for the temporal changes in tumor location and allows the possibility of dose escalation with a reduction in dose given to surrounding normal tissue.

Significant progress has been made using 4D CT scans to measure intrathoracic tumor motion. A number of studies have looked at the degree of motion of the primary lung cancer and have given recommendations for setup margin based on 4D CT results.^{14,15} This does not describe the motion of hilar and mediastinal lymph nodes involved with cancer, which is found in the majority of patients receiving definitive chemoradiation. Few studies have evaluated the motion of mediastinal and hilar lymph nodes using 4D CT scans¹⁶; prior studies have examined lymph node movement using fluoroscopic imaging, co-registered CT scans, and inhale and exhale CT scans.^{17,18,19}

We aimed to measure the amount of respiratory motion of mediastinal and hilar lymph nodes in comparison to the motion of the primary tumor in lung cancer patients using 4D CT scans from patients with intrathoracic malignancies and positive nodal disease in order to determine appropriate margin guidelines. In addition, we wanted to investigate whether knowledge of the primary tumor movement would predict the movement of the hilar and mediastinal lymph nodes.

Methods and Materials

Twenty consecutive patients, with prior 4D CT data available, having primary lung cancer and pathologically positive nodes who had undergone 4D CT scans in the treatment position with an alpha cradle immobilization as part of an IRB approved protocol were retrospectively analyzed (Table 1). The 4D CT data were captured using a 16-slice CT scanner (Brilliance 16, Philips Medical Systems) operated in ciné mode (couch stationary during scanning). Transverse slices of 1.5 mm thickness were acquired for a total thickness of 24 mm per couch position (16 × 1.5). The CT scanner, moving in a cranial-caudal direction, repeatedly acquired and reconstructed 25 images at each couch position, permitting data to be collected over 2 to

3 breathing cycles, depending on the patient's respiratory rate. During the CT scan, the patient breathing cycle was quantified using tidal volume measured using spirometry and a digital voltage signal from a "pneumatic bellows", a wraparound differential pressure sensor described in Lu *et al.*¹¹ In addition, patients underwent a fast helical scan using our standard clinical parameters. Each image was associated with a tidal volume measurement using a digital synchronization signal provided by the CT scanner. The tidal volume was subdivided into inspiratory and expiratory phases based on a local maxima/minima algorithm.²⁰ The CT scans were then sorted into four tidal-volume bins: peak expiration, peak inspiration, mid-expiration, and mid-inspiration. The details of the 4D CT techniques used at this institution have been previously described in more depth.^{11,21,20}

The 4D CT data sets divided into the four respiratory phases were exported to a Pinnacle 7.9u workstation (Philips, Madison, WI) with a research version of a 4D data manager and organ propagation tools. The primary tumor volume and pathologically positive nodes were manually contoured for the exhalation phase and the remaining phases were delineated with assistance from the automated propagation tools. The subsequent contours were reviewed and edited as required to precisely delineate the structures. In order to avoid individual discrepancies, all contouring was done by a single physician. The lymph node stations were identified and defined with the aid of a CT-based atlas (Fig. 1) from Chapet, *et al.*²² The primary tumor volume was contoured using a preset lung window setting (Window 1600, Level -300) and the lymph nodes were contoured using a preset thorax window setting (Window 400, Level 800). Only lymph nodes that were radiographically enlarged, greater than 1.5 cm, and distinguishable as discrete nodes were included. In total, for the twenty patients, forty lymph nodes were contoured at the following stations (number of nodes in parentheses): 2 (6), 3 (2), 4 (7), 5 (6), 6 (4), 7 (6), 8 (2), 10 (7).

Geometric and volumetric analysis was performed using the Pinnacle 7.9u program. For each region of interest the center of mass and volume was determined and recorded. The contours were then sent for further analysis to CERR, a Matlab-based treatment planning research tool.²³ Using CERR, the degree of movement at the edge of each region was calculated along with the movement of the geometric center. All statistical procedures were carried out using Matlab R2006a (Mathworks, Boston, MA), including a parametric statistics procedure used to test differences between means. Regression analysis was done using the least-squares regression method. The level of significance was set up at $P < 0.05$ (single tail).

Results

Primary tumor motion varied dramatically among patients. For the twenty patients, the mean primary lung tumor motion, calculated using the motion of the center of mass, was 1.1 mm in the medial-lateral (M-L) direction, 2.3 mm in the anterior-posterior (A-P) direction, and 5.2 mm in the superior-inferior (S-I) direction. The maximum observed motion was 25.4 mm in the superior-inferior direction (Fig. 2a). Calculating the mean motion using the edge of the region of interest showed a comparable degree of motion (2.3 mm M-L, 4.4 mm A-P, 5.9 mm S-I). The edge of region of interest technique consistently showed a greater degree of motion by a few millimeters compared with the center of mass technique, but followed the same trend in motion. For simplicity and clarity, only the center of mass results will be presented in the remainder of the paper. The edge of region of interest technique was more sensitive, consistently demonstrated a greater degree of motion by a few millimeters on average when compared to the center of motion, but for comparisons sake the rest of this article will focus on the center of mass alone. The primary tumors demonstrated no overall motion trend during the respiratory cycle for either the M-L or the A-P directions. All primary tumors were found to move inferiorly during inspiration.

Similarly, the contoured lymph nodes showed a dramatic variation in motion both among patients and within nodal stations. The lymph node mean motion was 2.6 mm in the M-L direction and 2.5 mm in the A-P direction; again, the greatest motion (mean, 5.2 mm) was observed in the S-I direction. The maximum motion for all lymph nodes was 14.4 mm in the S-I direction (Fig. 2b). There was no overall trend in motion during the respiratory cycle for either the M-L or the A-P directions. All lymph nodes were found to move inferiorly during inspiration, with 12.5% of nodes moving more than 1 cm and 45% moving at least 0.5 cm.

When comparing the movement of the lymph nodes within the individual stations there was a great deal of heterogeneity among patients and within the individual stations (Fig. 3 and 4). Multiple lymph nodes at all stations were positively identified, and many had greater than 6 nodes contoured for each individual station. The amount of motion varied dramatically between the stations, with lymph node station 6 demonstrating the least motion and lymph node stations 7 and 10 showing the greatest degree of motion. Table 2 demonstrates that the motion in both the M-L and A-P directions were similar for all nodal stations. However, motion was most pronounced in the S-I directions for nodal stations located below the carina.

The different nodal stations were then grouped to identify any overall differences in mean motion. The mediastinal nodes (stations 1–8) and the hilar nodes (station 10) were compared first. In the S-I direction, the hilar nodes moved 6.0 mm and the mediastinal nodes moved 4.3 mm, but the difference in the means was not significant ($P = 0.23$). In comparing supracarinal (stations 2–6) with subcarinal (stations 7–10), the M-L and A-P directions showed no significant difference between the two groups. In the S-I direction the means were significantly different ($P = 0.01$), with the supracarinal nodes moving 3.5 mm, compared to the subcarinal nodes that moved an average of 6.3 mm (Fig 5).

Subsequently we made comparisons between lymph node motion and both physiological parameters and tidal volume. Past studies have examined the hypothesis that individuals with decreased lung function as measured by spirometry would have decreased motion. In comparing the mean motion of patients with a FEV₁/FVC ratio of greater than 0.7 to those patients with a ratio of less than 0.7, no correlation was observed ($P = 0.29$). Next, comparisons were made between tidal volume and lymph node motion. Attempting to determine the degree to which tidal volume can explain motion we set up a least-squared regression. Using the least-squared regression methods, lymph node motion could be compared to tidal volume for all patients in our study (Fig 6b). The method gave an r^2 value of 0.75, indicating that with some degree of confidence that the variation in motion could be explained by tidal volume.

In comparing the primary tumor motion to the lymph node motion, no correlation was identified (Fig. 6a). Three-dimensional graphs of the individual patients demonstrated the lack of correlation between the primary lung tumors and the lymph nodes (Fig 7). As demonstrated in Figure 7a, patients in which a significant amount of motion was established in the primary lung tumor did not show similarly high amplitude of motion in their lymph node motion. Likewise, patients that had exhibited only small primary lung motion had lymph nodes that moved greater than 1 cm (Fig 7b). In comparison with the two motions no correlation was identified with amplitude, but all motion for both areas was in the inferior direction during inspiration.

Discussion

Discrepancies between actual tumor location and the area being targeted when planning with computed tomography are caused by both setup errors and organ motion. Because errors during radiation therapy can occur, it is important to determine the extent to which they do so in order to calculate more accurate margins of error. For intrathoracic tumors, organ motion is a major source of possible error. Several prior studies have examined the degree to which lung tumors

move during quiet respiration and all have shown a great deal of heterogeneity in this motion. Ekberg *et al.* found the motion to be approximately 2.4 mm in the M-L and a-P directions and, on average, 3.9 mm with a range of 0 to 12 mm.⁵ Likewise, the studies by Stevens *et al.* exhibited lung tumor motion ranging from 0 to 22 mm, concluding the motion with respiration was complex and not predictable by commonly performed imaging.^{8,9}

Estimating tumor motion using a CT scan obtained while the patient breaths freely, commonly referred to as three-dimensional (3D) treatment planning, can underestimate the motion of intrathoracic tumors.⁴ In using a four-dimensional (4D) CT scan, composed of 3D CT images acquired throughout the respiratory cycle, one can more accurately estimate the degree of motion.^{14,15} The use of 4D CT scans has been implemented clinically to aid in determining the motion of the primary lung tumors. However, the role of 4D CT scans to help determine the motion for mediastinal and hilar nodes has yet to be fully elucidated.

In this study, 4D CT scans from twenty patients were used to more accurately determine the degree of motion in pathologically positive mediastinal and hilar nodes. The data presented here shows that lymph nodes in both the mediastinum and hilum clearly exhibit motion during normal respiration. The motion observed was very heterogeneous for all patients at all lymph node stations. Overall, the mean motion of the center of mass was most pronounced in the S-I direction (average, 5.2 mm). The maximum motion for the twenty patients was 6.3 mm, 7.7 mm and 14.4 mm in the M-L, A-P, and S-I, respectively (Fig. 2a). A prior study by Jenkins *et al.*, using calcified lymph nodes as surrogates for malignant lymph nodes, showed a similar degree of heterogeneity, with the movement ranging from 0 to 24 mm.¹⁷ However, the study used no immobilization devices, which may have affected the tumor motion in some patients.

In comparing individual nodal stations, the motion ranged considerably both between the groups and within the individual stations (Fig. 3,4). The greatest amount of motion occurred in nodal stations 7 (subcarinal) and 10 (hilar); the least amount of motion occurred in nodal station 6 (paraortic). Sher *et al.* presented a similar trend, showing that both subcarinal and hilar nodes exhibited significant movement during respiration, a maximum of 23 mm for subcarinal and a maximum of 30 mm for hilar.¹⁶ Next, in examining the mean motion at different anatomic locations, no significant difference was evidenced between the motion observed in the mediastinal and hilar nodes. However, in comparing the supracarinal to the subcarinal, a significant difference was noted in the mean motion for the S-I direction ($P = 0.012$). The mean motion in the supracarinal and subcarinal was calculated to be 3.5 mm and 6.3 mm, respectively (Fig. 5). This finding is very important clinically for radiation oncologists attempting to predict the amplitude of motion in pathologically involved nodes. A smaller margin used for upper mediastinal nodes may not adequately cover subcarinal mediastinal nodes and hilar nodes, perhaps necessitating two separate margin recommendations for the two anatomic locations.

In comparing the primary tumor motion to the lymph node motion, both showed a wide heterogeneity of movement, most notably in the S-I direction. The maximum primary tumor motion found was 25.4 mm and the maximum lymph node motion in the same direction was slightly less at 14.4 mm. The amplitude of motion between the primary lung tumor and the lymph nodes showed no correlation. Patients may have exhibited significant amplitude of motion in the primary lung tumor, but little if any motion was found when examining lymph nodes within the same patient. The direction of movement was similar for all patients in the study, with both the primary tumor and the lymph nodes moving inferiorly with inspiration. Three-dimensional plots comparing the individual patients helped to further emphasize these trends (Fig. 7). The plots demonstrated that the motion of both tumors exhibited different trajectories. Both trajectories exhibited some degree of hysteresis, but the amplitudes did not correlate.

With no correlation observed between primary lung tumor motion and lymph node motion, these findings suggest that radiation oncologists need to look at both locations individually to properly assess the motion that may occur during treatment. Through the use of 4D CT scans, as demonstrated in this study, both movements can be quickly and accurately assessed on an individual basis. This assures that the lymph nodes are being targeted throughout the entire respiratory cycle, even in cases in which the lymph nodes were found to move a considerable distance. It also limits large margins being added for patients with very minimal movement.

Physiological parameters have been examined in prior studies in an attempt to more accurately predict movement for certain patients. The thought is that patients with poor pulmonary function would have decreased motion, due in part to reduced air movement and diminished contractions of the diaphragm. The comparison of patients' FEV₁/FVC ratios showed no difference between the groups, in agreement with prior studies.⁹ Our study did find correlation between increasing tidal volume and lymph node motion ($r^2 = 0.75$). This may be intuitive as patients with larger tidal volumes take larger breaths causing more motion to occur and would thus be more likely to have increased movement.

Although the use of 4D CT in this study did enable us to measure motion for both the primary lung tumor and pathologic lymph nodes, certain improvements could have enhanced the study. As noted prior, only lymph nodes that were easily identifiable as individual nodes were included and nodes were excluded that could not be fully visualized. Intravenous contrast could have led to easier distinction of nodes, especially in cases where nodes abutted vascular structure in the A-P window and near the hilum. In addition, repeating 4D CT scans during treatment would have been beneficial in order to determine the inter-fraction motion. The repeat scans would have provided a more comprehensive overview of the motion that occurs between fractions and in response to therapy, thereby facilitating further studies regarding the possible role for on-board imaging.

Conclusion

The study aimed to estimate the amount of movement of the different nodal stations and to compare the movement among the different stations with the gross tumor motion and physiologic parameters. In conclusion, 4D CT scans can be used to measure the motion for the primary lung tumor and pathologic lymph nodes encountered during the respiratory cycle. Both the primary lung tumor and the lymph node need to be examined to assess their individual degree of motion. Lymph nodes located below the carina exhibit a higher range of motion than nodes located higher in the mediastinum. The study demonstrated the need for individualized processes to assess the heterogeneous motion encountered in both areas and among lymph node stations.

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Figure 1. Anterior-Posterior view of mediastinal and hilar lymph node stations delineated by the Mountain and Dresler classification used by Chapet *et al*¹⁸ to develop a CT based atlas used to categorize lymph nodes. Reproduced with permission of Chapet *et al* and Elsevier Publishing.

Figure 2.

Histogram depicting the distribution of the primary tumor motion encountered during respiration for both the center of mass shown in dark gray and the edge of the region of interest shown in light gray. (COM – center of mass, Edge – edge of region of interest).

Figure 2b Histogram depicting the distribution of the lymph node motion encountered during respiration for both the center of mass shown in dark gray and the edge of the region of interest shown in light gray. (COM – center of mass, Edge – edge of region of interest).

Figure 3.

Anterior-posterior view of the trajectories of both primary tumors and pathologic lymph nodes. All patients primary tumors ($n = 21$) and lymph nodes ($n = 40$) are plotted at their approximate position based on location on helical CT.

Figure 4.
Anterior-posterior view of the trajectory of pathologic lymph nodes for all patients with positive nodes located at station number 7.

Figure 5.

Box and whisker plot comparison of the motion in mm of lymph nodes located above the carina (supracarinal, stations 1–6) to those located below the carina (subcarinal, stations 7–10). The horizontal line indicates the mean, the box covers 50% of the samples. Each data point is represented by a cross hatch.

Figure 6.

Scatter plot with best linear fit comparing the superior-inferior motion of individual lymph nodes to the superior-inferior motion of their primary tumors. The correlation coefficient (R-squared) was 0.75 with 0 indicating independent variables and 1 indicating a linear relationship. Figure 6b Scatter plot with best linear fit comparing the superior-inferior motion of individual lymph nodes to the tidal volume of all patients. The correlation coefficient (R-squared) was 0.75 with 0 indicating independent variables and 1 indicating a linear relationship.

Figure 7.
Anterior-Posterior view of the trajectory of both the primary tumor and pathologic lymph nodes encountered within individual patients (7a – Patient 8, 7b – Patient 6).

Table 1

Patient and Tumor Characteristics

Patient #	Age	Stage	Location	Histology	Pos. Nodes
1	74	T4N2M0	LUL	SCC	5,7
2	69	T2N2M0	L Lingula	Adenocarcinoma	4L
3	76	T2N2M0	LUL	SCC	8
4	53	T1N3M0	LLL	Adenocarcinoma	6,10R
5	69	T1N3M0	LUL	Adenocarcinoma	3,5
6	69	T1N3M0	RUL	SCC	3,4L,10R
7	66	T2N2M0	LLL	Adenocarcinoma	5
8	72	LD	RLL	SCLC	4R,7,10R
9	59	T2N2M0	LUL	SCC	4R,8
10	59	T4N2M0	RUL	Adenocarcinoma	2R,10R
11	60	T1N3M0	RLL	SCC	2R,10R
12	43	T3N2M0	RLL	SCC	2R
13	84	LD	RML	SCLC	7
14	73	T4N2M0	LUL,LLL	Adenocarcinoma	5,7
15	64	T3N3M0	RLL	SCC	2R,4R
16	46	LD	R Hilum	SCLC	6
17	41	LD	RUL	SCLC	2R
18	53	T2N2M0	LUL	Adenocarcinoma	5,6,10L
19	79	T2N2M0	RUL	SCC	2R,4L,7,10R
20	56	T2N3M0	LUL	Adenocarinoma	4R,5,6,7

R – right, L – left, SCC – squamous cell carcinoma, SCLC – small cell lung cancer, LD – limited disease, Pos. – positive

Table 2**Lymph Node Station Movement**

Nodal Stations	M-L	A-P	S-I
2	2.4 (0.5 – 3.6)	1.1 (0.1 – 3.6)	4.1 (2.0 – 6.8)
3	3.0 (2.9 – 3.1)	3.8 (2.3 – 5.2)	3.0 (1.7 – 4.4)
4	2.6 (0.5 – 5.1)	2.7 (1.2 – 7.7)	3.2 (0.6 – 12.3)
5	2.7 (0.4 – 6.3)	3.0 (0.5 – 7.8)	5.0 (0.6 – 10.0)
6	1.4 (0.1 – 2.4)	1.2 (0.1 – 1.6)	2.7 (1.4 – 4.1)
7	2.1 (1.1 – 3.2)	2.0 (0.4 – 3.9)	6.6 (2.3 – 10.1)
8	2.9 (1.4 – 4.6)	4.3 (2.9 – 5.7)	5.9 (2.1 – 9.7)
10	2.7 (0.1 – 4.9)	2.4 (0.9 – 5.6)	6.0 (1.4 – 14.4)

Mean motion in mm (min – max)

M-L – medial-lateral, A-P – anterior-posterior, S-I – superior-inferior, min – minimum motion, max – maximum motion