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Interfraction Displacement of Primary Tumor and Involved Lymph Nodes Relative to Anatomical Landmarks in Image-guided Radiotherapy of Locally Advanced Lung Cancer

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Abstract

Purpose—Image-guided radiotherapy for patients with locally advanced lung cancer relies on bony landmarks and carina or - if visible - the primary tumor (PT) for daily patient alignment, neglecting potential variations in the relative position of PT and involved lymph nodes (LN). This study analyzes PT and LN position changes relative to each other and relative to anatomical landmarks during conventionally fractionated radiotherapy.

Methods and Materials—In 12 patients with locally advanced non-small cell lung cancer PT, LN, carina and one thoracic vertebra were manually contoured on weekly 4D fan beam CTs. Systematic and random interfraction displacements of all contoured structures were identified in the three cardinal directions, resulting setup margins were calculated. Time trends and the effect of volume changes on displacements were analyzed.

Results—Three-dimensional displacement vectors and systematic/random interfraction displacements were smaller for carina than vertebra both for PT and LN. For PT, mean 3D displacement vectors with carina-based alignment were 7 mm/SD 4 mm versus 9 mm/SD 5 mm with bony anatomy ($p<0.0001$). For LN, smaller displacements were found with carina- (5 mm/SD 3 mm, $p<0.0001$) and vertebra-based (6 mm/SD 3 mm, $p=0.002$) alignment compared to using PT for setup (8 mm/SD 5 mm). Primary tumor and LN displacements relative to bone and carina were independent ($p>0.05$). Displacements between PT and bone ($p=0.04$), and between PT and LN ($p=0.01$) were significantly correlated with PT volume regression. Displacements between LN and carina were correlated with LN volume change ($p=0.03$).

Conclusions—Carina-based setup results in a more reproducible PT and LN alignment than bony anatomy setup. Considering the independence of PT and LN displacement and the impact of volume regression on displacements over time, repeated CT imaging even with primary tumorbased alignment is recommended in locally advanced disease.

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Conflict of interest: see statements.

Keywords

Lung cancer; Mediastinal lymph nodes; Interfraction displacement; Conventional radiotherapy; Image guidance

Introduction

Image-guided radiotherapy for patients with locally advanced lung cancer relies on anatomical landmarks or –if clearly defined– the primary tumor (PT) for patient setup. Current on-board imaging with planar x-rays or cone beam computed tomography (CBCT) often allows satisfactory identification of the PT, but fails to clearly visualize involved mediastinal lymph nodes (LN), resulting in potential misalignment of LN volumes. Accurate patient alignment during radiotherapy is also complicated by interfraction variations in position (1–5) and regression of both PT and LN volumes (6–8).

Various landmarks, such as skin tattoos, bony anatomy and carina (7,9,10) or implanted fiducials (11–13) have been investigated as surrogates for lung cancer positioning in image-guided radiotherapy. In general, bony anatomy- and carina-based setup resulted in less uncertainty than tattoos. Carina and fiducials were found to be more reliable than bone for tumor localization.

Only a few reports specifically analyze positional variations of involved LNs as part of the gross tumor volume. Recent publications investigated LNs either over a short time period at the beginning of radiotherapy only (5,6,14), used suboptimal imaging for LN assessment with CBCT (10), or employed respiration management techniques that are not widely used such as gating or active breathing control (7,8).

This study analyzed PT and LN position changes relative to each other and relative to anatomical landmarks during conventionally fractionated radiotherapy using state-of-the-art imaging with weekly free-breathing four-dimensional computed fan beam tomography (4D CT) with good detectability of PT and LN soft tissue boundaries. Different from other studies (15), time trends of the positional variations, and the influence of PT and LN volume regression and PT location on the observed positional variations were evaluated. In addition, safety margins were calculated for the different setup scenarios.

Materials and methods

Patient characteristics

In a prospective IRB-approved image acquisition study 12 consecutive patients with stage IIIA locally advanced non-small cell lung cancer were enrolled. All patients were treated according to department protocol with definitive conventional radiotherapy (1.8–2 Gy per fraction for five days a week to total dose between 64.8 and 70 Gy) combined with concurrent chemotherapy. Table 1 shows patient-specific clinical data.

Image acquisition and contouring

All patients underwent a 4D planning CT and weekly 4D CTs (Brilliance Big Bore, Philips Medical Systems, Andover, MA) with audiovisual biofeedback during their course of radiotherapy (16). Four to eight 4D CTs per patient (total of 65) with a slice thickness of 3 mm and 512×512 axial resolution (~1 mm pixel size) were acquired. Primary tumor (PT), involved lymph nodes (LN), a thoracic vertebra (V) and carina (C) were manually contoured by one physician on the 10 respiratory phases of each 4D CT (total of 650 3D CT scans) using a commercial treatment planning system (Pinnacle 8.1, Phillips, Fitchburg, WI). The

vertebra selected for contouring was in the central thoracic spine close to the involved lymph nodes and the carina. As no contrast was used, only well identifiable mediastinal lymph nodes (total 17) were contoured. To minimize any contouring variation, contours were copied between phases and manually corrected. In addition, templates of primary tumor and lymph nodes were created from each patient's initial 4D CT as contouring guidelines to reduce contouring variability between weekly scans. While all lymph nodes and the parts of the primary tumors next to mediastinum, diaphragm and chest wall were contoured in the default mediastinal window, primary tumors neighboring lung tissue were delineated in the lung window. The carina landmark was defined as a point at the most superior tip of the cartilaginous ridge between the main bronchi in the lung window. All contours were reviewed by a second physician.

Data analysis

Three dimensional displacement vectors, systematic/random displacements and resulting margins—To analyze the interfractional positional variability of contoured structures for each patient first the average centroid positions of primary tumor, lymph nodes and vertebra were calculated for each 4D CT by determining the geometric center of each structure for each breathing phase in the three cardinal directions and averaging these positions over the 10 breathing phases. Similarly, for calculating the average carina position, the carina point coordinates were averaged over the 10 breathing phases for each 4D CT. After assessing the distances between the average centroid positions of PT/LN, PT/V, PT/C, LN/V and LN/C per 4D CT of each patient, variations in the distances between these centroid positions between the initial planning scan (reference) and the subsequent scans during therapy were determined for lateral (x), anteroposterior (y) and craniocaudal (z) directions by subtracting the distance between two average centroids for each weekly 4D CT from the distance measured on the reference planning scan. From these results, three dimensional (3D) displacement vectors were calculated as the square roots of the summed squared displacements in the 3 directions for each 4D CT and each patient. Displacements for all 3 directions and for 3D displacement vectors were averaged over all scans of each patient and over all patients. The dependence of displacements on PT location was analyzed.

Systematic and random displacements were calculated according to (17). Systematic displacements were defined as the standard deviations of the individual patients' mean centroid displacements averaged over all 4D CTs per patient in the three cardinal directions. Random displacements were calculated as the square root of all patients' average variances that were derived from the individual patients' standard deviations of the average centroid displacements per 4D CT in the three cardinal directions averaged over all 4D CT scans. Systematic and random displacements were used to calculate setup margins for PT-, V- and C-based image guidance according to van Herk's formula corrected for penumbra in lung tissue (18). The setup margins do not include variations in respiratory motion or contouring variability. Both are presumed to be small assuming motion-inclusive planning (19) and having one observer contour all regions of interest using above described measures to reduce delineation errors.

Time trends of displacements—To identify positional time trends, week-to-week displacements of PT/V and PT/C, as well as PT/LN, LN/V and LN/C relative to the reference scan were analyzed. In addition, potential correlations between PT and LN displacements relative to carina and vertebra were evaluated.

Association of displacements with volume regression—Volume changes of PT and LN, regression rates and the influence of PT and LN volume changes on displacements were investigated.

Statistics

Differences in 3D displacement vectors, systematic and random displacements, and tumor location between PT/V and PT/C, as well as between PT/LN, LN/V and LN/C were analyzed for significance using a Wilcoxon signed rank test. Longitudinal data analysis of PT and LN positions over the treatment weeks, their association with volume change, and their variability over time was estimated using a repeated measures model with compound symmetric covariance matrix for the correlated observations. Correlation of variability of PT and LN distance from carina or vertebra was tested using a likelihood ratio test. An asymptotic chi-square distribution was used to determine the significance of the test. Statistically significant results were assumed for $p < 0.05$. Analyses were done in SAS 9.2.

Results

Three dimensional displacement vectors, systematic/random displacements and resulting margins

The analysis of mean 3D displacement vectors shows that carina-based setup was more reproducible than vertebra for alignment of the PT (7 mm/SD 4 mm versus 9 mm/SD 5 mm, $p < 0.0001$). For LN alignment, smaller displacements were found with carina- (5 mm/SD 3 mm, $p < 0.0001$) and vertebra-based (6 mm/SD 3 mm, $p = 0.002$) setup compared to PT (8 mm/SD 5 mm). An example of the positional variability between PT, LN and carina is shown in Figure 1. The frequency of interfraction displacements $> 3/5$ mm is shown in Table 2. Carina-based displacements > 5 mm were less frequent than bony anatomy-based displacements for both PT and LN. Displacements of PT relative to V and C were larger for lower than middle and upper lobe tumors ($p = 0.04$ for V and $p = 0.13$ for C), but not relative to LN ($p > 0.05$). Systematic/random interfraction displacements were 2 – 4 mm/3 – 4 mm between PT and LN, 3 – 7/2 – 3 mm between PT and V, 2 – 5/2 – 3 mm between PT and C, 3 – 6/2 – 3 mm between LN and V, and 2 – 4/2 – 4 mm between LN and C with ranges showing the variations in the cardinal directions (Fig. 2). Significant differences were observed for systematic/random displacements between PT/LN and LN/V in ap-direction ($p < 0.05/p < 0.05$), and between PT/LN and LN/C in ap ($p < 0.01/p < 0.05$) and lateral direction ($p < 0.001/p < 0.05$).

The resulting margins to cover PT and LN displacements were smaller for carina- than vertebra-based alignment. Using PT to align LNs still resulted in margins of 10 – 14 mm, compared to 11 – 18 mm for vertebra-, and 8 – 15 mm for carina-based LN alignment (Fig. 2). Therefore, using carina for alignment of both primary tumor and lymph nodes is preferable to both bony anatomy-based and primary-tumor based setup in this cohort.

Time trends of displacements

Figure 3 shows the change in average 3D vector distance between PT, LN and landmarks during therapy. While LN/V and LN/C remained relatively stable with 6 and 5 mm 3Ds displacement, respectively, PT/LN, PT/V and PT/C increased over time reaching average 9, 11 and 10 mm displacements in week 5. A significant time trend was observed for PT/C ($p < 0.03$), a borderline significant time trend for PT/V ($p < 0.09$). The variability in PT and LN displacements relative to carina and vertebra were not significantly correlated.

Association of displacements with volume regression

The average initial volume on the 4D CT planning scan was 77 cm³ (range 7–392 cm³) for PT and 5 cm³ (range 1–15 cm³) for LN. The mean volume after 5 weeks of treatment as a percentage of the initial volume was 41% (range 29 – 95%) for PTs and 57% (range 26 – 86%) for LNs. The rate of tumor regression was 1.7% for PT and 1.2% for LN ($p > 0.05$).

Figure 4 shows the average weekly PT and LN regression. Displacements of PT/V and LN/C were significantly related to the respective volume changes of PT and LN ($p=0.04$ and 0.03). Variations in the distance of PT/LN over time correlated with PT ($p=0.01$), but not with LN volume regression.

Discussion

This work identified carina to be more a more reliable landmark than bone for set up of PT and LN. In addition, significant time trends and volume dependence of positional variations were observed.

Displacements relative to bony anatomy and carina

While the benefits of image-guidance are well documented (11), little information is so far available on LN displacement and the accuracy of bone- versus carina-based setup. Average PT displacements of 9 mm relative to bone in our study were larger than the displacements of 6 mm found by v. Elmpt et al. (14) and 5 mm observed by Juhler-Nøttrup et al. (7). Both studies analyzed mostly upper lobe tumors where less PT displacement is observed than for the predominantly lower lobe tumors in our study. In addition, v. Elmpt investigated displacements only for the first 2 weeks of treatment, whereas Juhler-Nøttrup's and our study evaluated a complete course of treatment which is necessary to fully appreciate systematic trends as described in the present work. Displacements of LN relative to bone of 6 mm in our study were similar to reports of 4–6 mm in the literature (5,7,14).

Few studies investigated carina as a landmark for patient setup. Similar to our study, other reports observed more reliable alignment for PT (9), LN and combined PT-LN (10) using carina for setup. These reports (9,10) investigated target coverage after automated or manual CBCT registration and matching of the anatomy of the day with planning ITVs and PTVs. A signature limitation of CBCTs is the identification of soft tissue boundaries in low contrast areas like the mediastinum. For this reason higher quality respiration-correlated fan beam CTs were used in the present study. Using carina instead of vertebra for setup in our study reduced margins from 10–20 mm to 8–14 mm for PT and from 11–18 mm to 8–15 mm for LN.

Relative displacement of PT and LN

Using soft tissue-based image guidance strategies to align the primary tumor does not necessarily entail appropriate coverage of involved lymph nodes. Among the few studies that investigated simultaneous PT and LN alignment, a comparable magnitude of 3D PT/LN displacements was measured with 7 mm in Juhler-Nøttrup's study (7) compared to 8 mm in the present study. Relative displacements between PT and LN were found to be similar to displacements of PT and LN alone relative to bone which was thought to be caused by PT and LN displacements in different directions (7). Similar observations were also made in our work where the displacements of PT and LN relative to landmarks were independent. While v. Elmpt et al. (14) noticed a weak correlation between PT and LN displacement, only a short period of time was investigated. In our study, both carina and bone were identified as leading to an on average more reliable LN alignment than PT-based setup. This finding is supported by Mohammed et al. (15) who registered repeated 4D CTs using bone, PT and PT-LN and measured geographic miss based on the initial ITV. The authors found that for LN coverage, bony anatomy or combined PT-LN registration are more accurate than PT-based setup. Carina was not investigated in this study, but showed even better LN alignment than bone or PT in our study.

Volume regression and time trends

Primary tumor regression is well documented (3), however, only few reports have investigated lymph node volume reduction over a whole radiotherapy series. Juhler-Nøttrup et al. (7) reported a LN volume reduction of 34% which is of a similar magnitude as the mean 43% reduction in this series. In a similar analysis of breath hold patients, LN volume reduction was 37% after 5 weeks of therapy (8). Reports with shorter observation times did not identify relevant LN volume changes (6,14). PT and LN volume change was significantly correlated with relative displacements of PT/LN, PT/V and LN/C. A correlation between PT volume regression and positional variability had been observed before (2), while the effect of LN volume reduction on the relative LN position has not been investigated so far.

This study also found significant time trends for PT-related displacements relative to bone, carina and LN. Repeated imaging and, if indicated, re-planning, particularly in patients with primary tumors in the lower lobes should be considered to reduce targeting errors and improve the outcome in lung cancer patients (20, 21).

The results of this study depend to a large extent on image and contouring quality. Although we used 4D CTs for this analysis, imaging artifacts may exist. Biofeedback was employed to reduce breathing irregularities that may compromise image quality (16). Also, instead of choosing a time-average phase such as the 30% phase for the present evaluation, the average geometrical position calculated from all 10 breathing phases was assumed to be less sensitive to irregular breathing. Delineation errors, particularly using non-contrast CT scans, cannot be ruled out. To reduce delineation errors, only well-demarcated mediastinal lymph nodes, not hilar lymph nodes, were selected for this analysis. The generation of contouring templates of primary tumors and lymph nodes for each patient, the ability to copy contours between the phases of each 4D CT scan, independent review by a second physician and the availability of diagnostic imaging for reference were presumed to minimize contouring variability. While population-averaged positional variations are investigated in the present studies, an individualized decision on the correct setup strategy appears important. Carina was found to be the on average more reliable surrogate in this population, use of any surrogate is, however, always inferior to alignment based on the tumor components themselves. Also, vertebra-based alignment might be advantageous in individual patients. In addition, depending on the size and location of the primary tumor next to critical structures, primary tumor-based setup with reduced margins around the primary tumor itself might be desirable to spare surrounding normal tissue. Larger patient cohorts are needed to identify characteristics favoring either set up modality.

Conclusion

Lymph node displacement relative to the primary tumor is a relevant source of potential geographic miss requiring considerable safety margins. Using carina instead of bony anatomy for patient setup, results in a more reproducible primary tumor and lymph node alignment on average. Time trends and the influence of volume regression on displacements over time indicate the importance of re-imaging to account for interfractional variability.

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Summary

In 12 patients with locally advanced non-small cell lung cancer, displacements of primary tumor (PT), involved lymph nodes (LN), carina and one thoracic vertebra were investigated on weekly 4D fan beam CTs. Carina-based setup resulted in a more reproducible alignment of PT and LN than bony anatomy setup. Displacements were significantly correlated with PT and LN volume regression.

Figure 1.

Example of displacements between primary tumor, lymph nodes and carina A. Anatomy during treatment planning showing primary tumor PT, carina and lymph nodes (*) in the same coronal plane. B. Anatomy in week 7 displaying carina and lymph nodes unchanged to A. C. Anatomy in week 7 with primary tumor shift posterior to plane B indicating that primary tumor is not a good surrogate for lymph node alignment in this patient.

a. Systematic displacements

b. Random displacements

c. Margins

Figure 2.
Systematic and random displacements and margins in the three cardinal directions.

Figure 3.
Average 3D displacements per week.

Figure 4.
Average volume change of primary tumors (PT) and lymph nodes (LN) relative to week 0 reference scan (100%) with standard deviations.

Table 1

Patient characteristics

Patient	# Weekly Scans	PT Location	LN Location	# LN	Stage	PT Volume (cm ³)	LN Volume (cm ³)	Respiratory motion (mm)
1	5	R UL	4R	1	IIIA	12	2	5
2	5	R LL	4 R/L	2	IIIA	392	4, 2	9
3	4	R LL	4R	1	IIIA	55	2	7
4	4	R LL	4R	2	IIIA	75	1, 2	6
5	5	L UL	2L	1	IIIA	31	8	0
6	4	L LL	4 R/L	1	IIIA	78	8	2
7	5	R ML/LL	7	1	IIIA	179	8	1
8	6	R UL	4 R	2	IIIA	7	9, 1	4
9	5	L UL	4R/2L	2	IIIA	33	3, 3	2
10	8	R LL	4R	1	IIIA	10	3	5
11	6	R LL	4R	1	IIIA	13	1	8
12	8	R UL/ML	1R	2	IIIA	117	15, 1	1

R: right; L: left; LL: lower lobe; ML: middle lobe; UL: upper lobe. Extent of respiration was measured on the initial planning scan for the primary tumor.

Table 2

Interfraction displacements of more than 3 mm and 5 mm (65 4D CT scan total).

	Percentage of fractions with displacements larger than									
	3 mm					5 mm				
	x	y	z	3D		x	y	z	3D	
PT/LN	28	45	49	87		15	28	32	64	
PT/V	32	40	54	87		11	29	37	75	
PT/C	23	54	49	85		5	29	26	62	
LN/V	28	34	37	87		14	15	18	51	
LN/C	23	18	18	62		11	8	10	40	