



UvA-DARE (Digital Academic Repository)

Multimodality approach towards individualized non-small cell lung cancer treatment

Schaake, E.E.

Publication date
2014

[Link to publication](#)

Citation for published version (APA):

Schaake, E. E. (2014). *Multimodality approach towards individualized non-small cell lung cancer treatment*. [Thesis, externally prepared, Universiteit van Amsterdam].

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

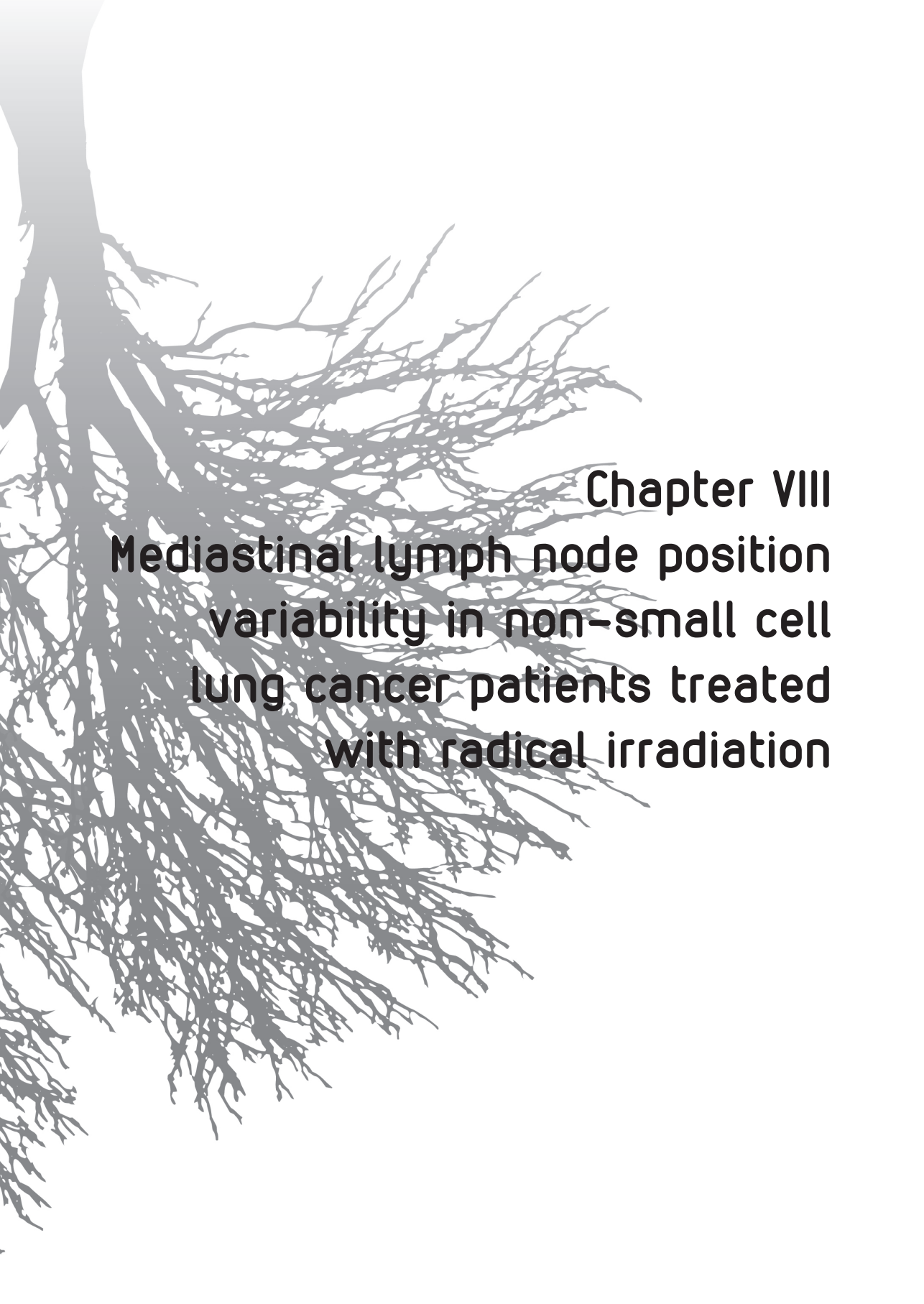
Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.



E.E. Schaake
J.S.A. Belderbos
W.A. Buikhuisen
M.M.G. Rossi
J.A. Burgers
J.-J. Sonke

Radiation and Oncology,
October 2012



Chapter VIII
Mediastinal lymph node position
variability in non-small cell
lung cancer patients treated
with radical irradiation

ABSTRACT

Background and purpose | Knowledge on mediastinal lymph nodes position variability is lacking. In this study we quantified the variability over the irradiation course in non-small cell lung cancer (NSCLC) patients.

Methods | A 0.35x5 mm gold fiducial marker was inserted in mediastinal lymph nodes of 14 stage III NSCLC patients. A respiration correlated 4D planning CT (PLCT) and daily 4D Cone Beam (CB)CT-scans were acquired. To calculate the systematic and random baseline variations, and respiratory motion variability of the lymph nodes all CBCT scans were first registered to the bony anatomy in the PLCT. Patient population statistics of the peak-to-peak amplitude and time averaged mean position relative to the bony anatomy were calculated.

Results | The average peak-to-peak amplitude was 0.21 cm, 0.52 cm and 0.20 cm in de Left-Right, Cranial-Caudal and Anterior-Posterior direction respectively, while the amplitude variability was ≤ 0.1 cm in each direction. Inter-fraction lymph node baseline variation was 0.21/0.2 cm, 0.34/0.23cm and 0.17/0.15 cm systematic/random. PTV margins for these variations were 0.92 cm, 1.24 cm, 0.82 cm if for an online bone match and could be reduced to 0.77 cm, 0.82 cm and 0.86 cm for an online carina match.

Discussion | Substantial and anisotropic systematic and random mediastinal lymph node baseline variation was found in NSCLC patients indicating that non-uniform margins could be beneficial.

INTRODUCTION

The life expectancy of lung cancer patients is strongly correlated with the locoregional extension of the tumor in the mediastinal lymph nodes. In case of mediastinal lymph node metastases, standard treatment consists of concurrent chemo- radiotherapy of the tumor and involved mediastinal lymph nodes. Radiotherapy of this region demands specific technical skills as considerable geometrical uncertainties are associated with radiotherapy of lung cancer due to set-up errors: misalignment of the patient relative to the treatment iso-center (1), baseline variation: displacement of the target's mid-position relative to the bony anatomy (2) and respiratory motion (3). Generous safety margins are required to account for such geometrical uncertainties in the absence of adequate correction strategies exposing nearby organs at risk to high doses resulting in considerable toxicity (4-8). With current combined chemo- radiotherapy regimens for locally advanced lung cancer esophagus toxicity is one of the main side effects, due to its proximity to involved lymph nodes.

Image guided radiotherapy (IGRT) (9) has been developed to reduce geometrical uncertainties by acquiring images of the patients anatomy just prior to treatment, comparing these with the anatomy during treatment planning to assess target misalignments and making correction typically through a couch shift. For locally advanced lung cancer, however, differential motion between pathological lymph nodes and primary tumor limits the potential of couch shift based correction strategies to reduce these geometrical uncertainties. Moreover, while position variability of the primary tumor has been extensively studied (5), involved lymph nodes are difficult to visualise on IGRT imaging modalities such as Cone Beam CT (CBCT), due to the lack of contrast. Therefore, it is unclear if current Planning Target Volume (PTV) margins of involved lymph nodes are adequate to account for its variability.

There is a clear need to quantify the inter-fraction baseline variability and respiratory induced amplitude variability of mediastinal lymph nodes. The use of implanted fiducial markers facilitates the visualization of the nodes in the imaging modalities available in the treatment setting. The aim of this study was therefore to determine the mediastinal lymph node position variability using implanted gold fiducial markers and determine corresponding safety margins.

MATERIALS AND METHODS

A single center prospective cohort study, opened in August 2010, was performed in NSCLC patients treated with radical radiotherapy to determine mediastinal lymph node position variability using fiducial markers (from now on referred to as marker). Patients who were medically fit (WHO 0-2), 18 years or older, without prior mediastinal surgery or chest irradiation and who underwent trans-oesophageal endoscopic ultrasound-

guided mediastinal lymph node aspiration (EUS-FNA) (10) for diagnostic purpose and subsequent radiation therapy or chemoradiation for primary treatment, were eligible for inclusion within this study. Written informed consent was obtained from all patients according to ICH/GCP and national and local regulations. This study was approved by the institutes' medical ethical committee.

The endpoint of the study was to quantify the inter-fraction baseline variations and variation of respiratory motion amplitude of lymph nodes over the course of radiotherapy, in NSCLC patients.

Marker placement using EUS-FNA

The EUS-FNA procedure was performed under intravenously administered short acting propofol sedation. After obtaining cytology of a suspicious lymph node on (PET-) CT, a single marker was inserted, extending the total procedure time with two to five minutes. The sterile 0.35 mm by 5.0 mm gold marker (Visicoil by RadioMed, Barlett, USA) was preloaded into a 22-gauge EUS-FNA needle with the stylet retracted slightly to accommodate the marker and sealed off with sterile bone wax. The needle was then inserted into the working channel, advanced into the desired lymph node under EUS guidance and the marker was inserted into the lymph node by carefully advancing the stylet (Figure 1).

Treatment

Every patient received standard radical Intensity Modulated RT (IMRT) conform the tumor stage; treatment schedules were not adapted for this study. A 4 dimensional (4D) CT-scan with intravenous contrast (0.3 cm slice thickness) was made and subsequently a Mid-Ventilation CT scan (MidV CT) or Mid-Position CT (MidP CT) scan was reconstructed from the 4D CT scan (11) for delineation of the targets and organs at risk, and treatment planning. In a MidV CT a frame out of a 4D CT scan closest to the time average mean tumor position is used. A MidP scan is a 3D scan reconstructed using deformable registration based motion compensation with the complete anatomy in the time -averaged mean position. Patients were treated in supine position, to a dose of 66 Gy in 24 fractions with an overall treatment time of 32 days using 10 MV photon beams. Two patients received 60Gy in 30 fractions and one patient received a dose of 51 Gy in 17 fractions as the mean lung dose was too high otherwise. The involved irradiation fields encompassed the primary tumor and pathological lymph nodes. The Gross Tumor Volume (GTV) and organs at risk (OAR) were delineated according to the institutional protocol and subsequently PTV margins were added to the GTV (no margins for microscopic disease). For the lymph nodes the current margin (GTV-PTV) is 12 mm, irrespective of the motion of the lymph node, while the GTV-PTV margin for the primary tumor is 12 mm + 0.25 times the GTV's peak-to-peak amplitude observed in the 4D CT. Daily 4D cone beam CT scans were acquired using Elekta Synergy 4.2 or 4.6 (Elekta Oncology Systems Ltd., Crawley, UK) augmented with in-house developed software. The imaging dose per scan was about 2 cGy and 4D CBCT scans were reconstructed in 10 equidistant phases with 2x2x2 mm³ voxel

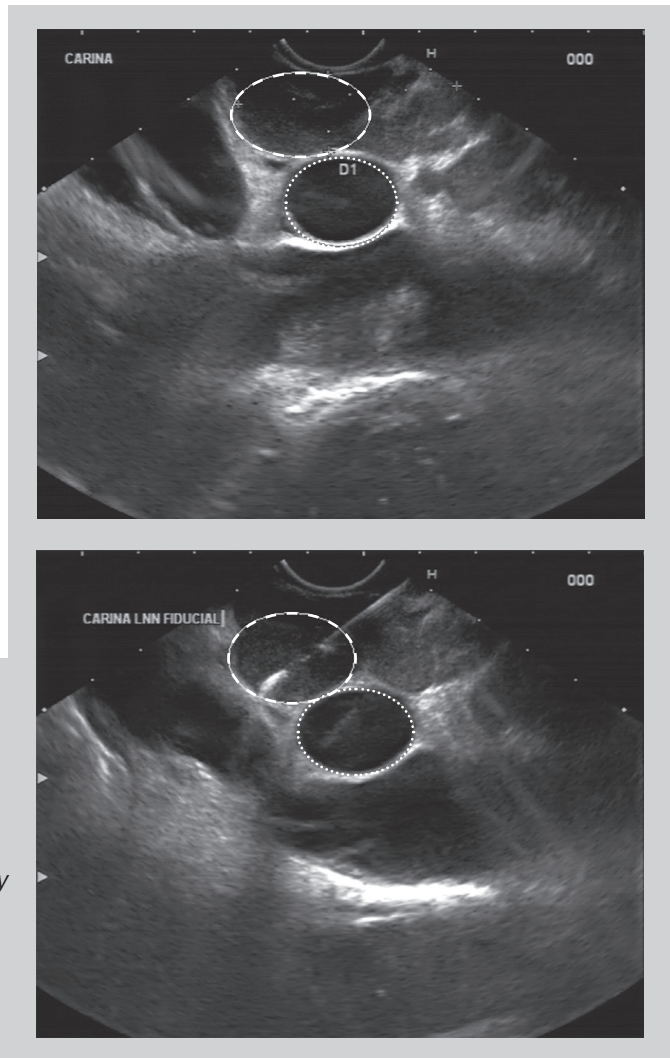


Figure 1. Marker placement under endoscopic ultrasound guidance.

1a. The lymph node is outlined with the dashed ellipse, the pulmonary artery with the dotted ellipse.

1b. The marker is inserted in the lymph node while the needle is being retracted.

size. An online set-up correction protocol based on bony anatomy (vertebral bodies at the level of the high dose region) was used to minimize the patient set-up error and to detect relevant anatomical changes within the thorax.

Lymph node position variability analysis

For this study the position of each individual marker was registered in each phase of each 4D CBCT scan to the planning CT using a marker tailored chamfer matching algorithm yielding the lymph node trajectory (position of the lymph node marker over the different breathing phases) relative to the planning CT marker position. Additionally, in a similar way the carina displacements were quantified by a local rigid 4D grey-value registration.

To quantify baseline variability, first the time-weighted mean lymph node position (averaged over the 10 phases taken into account the relative time spend in each phase of the breathing cycle) was calculated. Subsequently, the result of the bony anatomy registration was subtracted from the time averaged mean lymph node marker position to obtain the lymph node baseline shift for that fraction. Inter-fractional baseline variability was quantified in terms of group mean, systematic errors (Σ), and random errors (σ). Additionally, the lymph node peak-to-peak breathing amplitude was calculated by the excursion of the trajectory in the LR, CC and AP direction. Subsequently, the inter-fraction trajectory shape variations were quantified over the all the scans per patient and over the patients and compared to the lymph node trajectory in the 4D planning CT.

Margins

The GTV-PTV margin to ensure that the lymph nodes receive at least 95% of the prescribed dose for 90% of patients when all geometric uncertainties are included were calculated for all three directions using the following Margin recipe (12)

$M = 2.5 \cdot \Sigma + 1.64 \cdot (\sqrt{[\sigma^2 + A^2/9] + \sigma_p^2} - \sigma_p)$. With Σ the overall standard deviation (SD) of the systematic errors, σ the overall SD of the random errors, A the peak-to-peak amplitude of the lymph node respiratory induced motion and σ_p , describing the width of the penumbra. The overall systematic and random errors were calculated as $\Sigma = \sqrt{[\Sigma_B^2 + \Sigma_T^2 + \Sigma_L^2 + \Sigma_I^2]}$ and $\sigma = \sqrt{[\sigma_B^2 + \sigma_L^2 + \sigma_I^2]}$, where the subscript $_B$ refers to baseline variation as quantified in this study, $_T$ refers to target definition uncertainty estimated at 2 mm (1SD), $_L$ refers to localization accuracy and $_I$ refers to inter-fractional variability. The latter two were taken from Sonke et al (13). σ_p was set to 0.32 cm (14).

Higgins et al.(15) suggested to use the carina as a surrogate for the lymph node position. Therefore, the residual lymph node position variability relative to the time averaged mean carina position were also quantified and resulting margins were calculated. The time averaged mean carina position was determined similar to the marker registration except that grey value registration was used instead of chamfer matching.

Marker Migration

Using an implanted marker as a surrogate for the lymph node position, assumes that the position of the marker relative to the lymph node is constant, i.e., implanted markers do not migrate. To measure possible migration the time averaged mean marker position was compared to the position of its surrounding tissue in the CBCT scans of the last two treatment days per patient. To that end, 4D CBCT-to-planning CT grey-value registration of the surrounding tissue was performed using a shaped ROI. The marker was excluded from the ROI to minimize its influence on the registration result.

Table 1. Patient Characteristics

| Patient characteristics | All patients (n = 16) N= or Mean |
|---|--|
| Age in years | 64 (50-85) |
| Gender | |
| Male | 10 |
| Female | 6 |
| Stage | |
| IA | 0 |
| IB | 1 |
| IIA | 1 |
| IIB | 1 |
| IIIA | 8 |
| IIIB | 4 |
| IV Left | 1 |
| Histology | |
| Adenocarcinoma | 7 |
| Squamous cell carcinoma | 4 |
| Undifferentiated NSCLC | 5 |
| Radiation dose | |
| 51 Gy (17x 3 Gy) | 1 |
| 60 Gy (30x 2 Gy) | 2 |
| 66 Gy (24 x 2.75 Gy) | 13 |
| Lymph node stations with marker (n=16) | |
| II Left | 2 |
| IV Left | 2 |
| V | 2 |
| VII | 9 |
| VIII | 1 |
| Concurrent chemotherapy | 13 |

RESULTS

From September 2010-August 2011 a total of 16 patients were included for the first analysis. Patient and tumor characteristics are listed in Table 1. The EUS guided marker placement occurred without complications and no markers were lost during placement or treatment. The 16 markers were inserted in five different lymph node stations: two markers in lymph node station II, two markers in station IV, two markers in station V, nine markers in station VII and one in station VIII.

Fourteen out of 16 patients finally received radical irradiation of 51-66 Gy for NSCLC. The two patients not receiving radical irradiation were excluded from further position variability analyses; both patients had a marker in lymph node station VII. All inserted markers were well visible on planning CT and CBCT and an average of 22 CBCT scans were acquired per patient (range 17-24).

Lymph node baseline variation

An example of lymph node base line variation is shown in Figure 2, where both the exhale and inhale position of the inserted marker is considerably displaced following bony anatomy alignment. The systematic baseline variation over the 14 patients was 0.21 cm, 0.34 cm and 0.17 cm in the LR, CC and AP direction respectively while the random baseline variation was 0.20 cm, 0.23 cm, 0.15 cm (Table 2A).

The mean (range) peak-to-peak amplitude of the lymph nodes during treatment was 0.20 cm (0.10-0.32 cm), 0.52 cm (0.11-1.06 cm) and 0.21 cm (0.11-0.30 cm). Amplitude variability was calculated by subtracting the amplitude of the 4D PLCT from the average amplitude of the CBCT per patient. The group mean amplitude differences were -0.03 cm in LR, 0.15 cm in CC and -0.03 in the AP direction. The systematic differences were 0.07 cm, 0.32 cm and 0.10 cm respectively and somewhat larger than the random amplitude variability over the treatment course of 0.11 cm, 0.13 cm and 0.13 cm respectively.

Margins were calculated to account for the residual geometrical uncertainties following an online bony anatomy correction strategy to cover the lymph nodes of 90% of the patients with 95% of the prescribed dose. Figure 3 depicts the required CTV-to-PTV margins as a function of the lymph node peak-to-peak amplitude. For the average peak-to-peak amplitude over the 14 patients, these margins were 0.92 cm, 1.24 cm and 0.82 cm in the LR, CC and AP direction respectively. Using the carina as a surrogate for lymph node location significantly reduced the systematic residual lymph node position variability in the CC direction ($p=0.0007$), and the random residual lymph node position variability with a trend towards significance in the LR ($p=0.051$) and CC ($p=0.077$) direction (Table 2B). This could lead to a margin reduction to 0.77 cm, 0.82 cm in the LR and CC direction and a very small increase to 0.86 cm in the AP direction for the average peak-to-peak amplitude. As a function of the respiratory amplitude, the curves in all three directions are very similar to the AP curve in Figure 3.

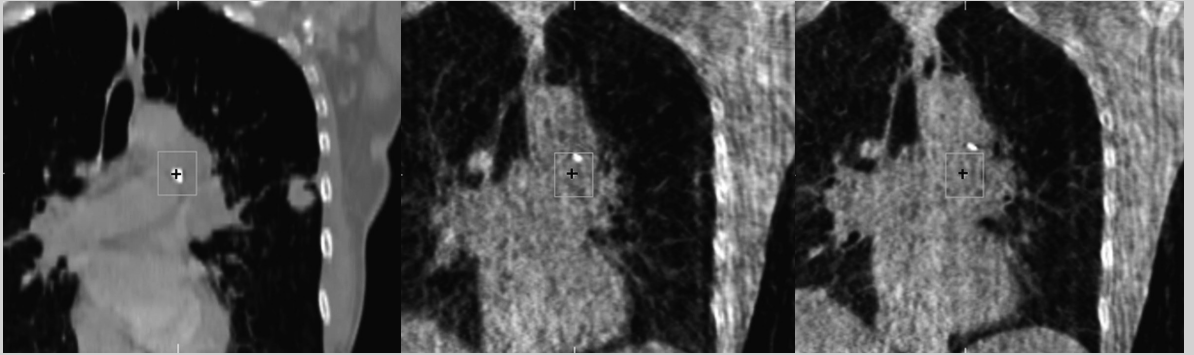


Figure 2. Example of marker baseline variation. The planning CT (left column) and CBCT (exhale middle column, inhale right column) registered to the bony anatomy depicted in coronal plane. The center of the mass of the marker in the planning CT is marked by a black marker to show the displacement on CBCT.

Table 2A. Lymph node position variability relative to the bony anatomy

| | Left-Right | Cranial-Caudal | Anterior-Posterior |
|------------------------------|--------------|----------------|--------------------|
| Group mean | 0.02 cm | 0.09 cm | 0.04 cm |
| Systematic (Σ : 1SD) | 0.21 cm | 0.34 cm | 0.17 cm |
| Random (σ : 1SD) | 0.20 cm | 0.23 cm | 0.15 cm |
| Amplitude average | 0.20 cm | 0.52 cm | 0.21 cm |
| Range | 0.10-0.32 cm | 0.11-1.06 cm | 0.11-0.30 cm |
| Online corrected margin | 0.92 cm | 1.24 cm | 0.82 cm |

Table 2B. Lymph node position variability relative to the carina

| | Left-Right | Cranial-Caudal | Anterior-Posterior |
|------------------------------|------------|----------------|--------------------|
| Group mean | 0.04 cm | 0.04 cm | 0.07 cm |
| Systematic (Σ : 1SD) | 0.14 cm | 0.12 cm | 0.21 cm |
| Random (σ : 1SD) | 0.15 cm | 0.17 cm | 0.11 cm |
| Online corrected margin | 0.77 cm | 0.82 cm | 0.86 cm |

Marker migration assessment

To quantify possible marker migration, the residual time averaged marker displacement was determined relative to the surrounding tissue for the last two scans of each patient. The average (1 SD) displacement over all patients was 0.06 (0.10) cm, 0.04 (0.14) cm and 0.04 (0.12) cm in the LR, CC and AP direction respectively. Using the difference between the two last scans per patient, the measurement error in the migration numbers above was estimated at 0.11 cm, 0.17 cm and 0.12 cm in the LR, CC and AP direction

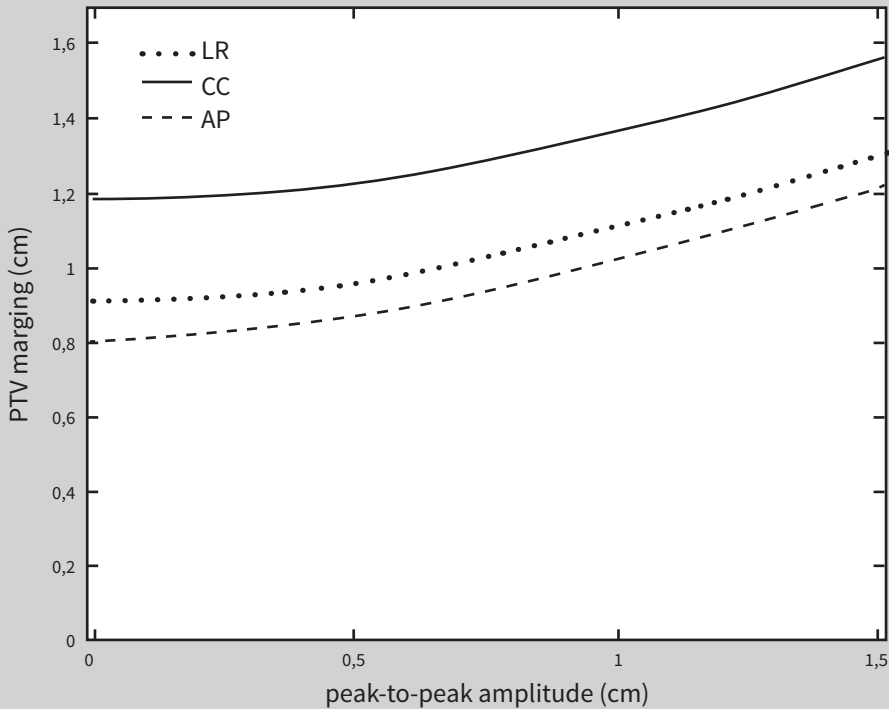


Figure 3. PTV margin as a function of lymph node peak-to-peak amplitude for the Left-Right (LR), Cranial-Caudal (CC) and Anterior-Posterior (AP) direction, for an online bony anatomy based correction strategy.

respectively (1 SD). This indicates that marker migration was negligible in this study. Note that this measurement error is the result of a marker registration and soft-tissue registration. The registration error in the marker position, having a higher contrast than the soft tissue is thus likely to be much smaller. In one patient, considerable anatomical changes over the course of treatment made accurate local rigid soft tissue registration unfeasible (figure 4). This patient was excluded from the migration analysis. As no migration in other patients was observed and actual lymph node baseline shift in this patient could be clearly visualized, the patient was not excluded from the position variability analysis.

DISCUSSION

This article is the first to report on actual mediastinal lymph node baseline variability. In this study markers were inserted under EUS guidance and visualised by daily CBCT scans making precise quantification of lymph node baseline variability possible. Placement of the markers under EUS guidance was fast and without complications. Most lymph node baseline variability was seen in the Cranial-Caudal direction. PTV

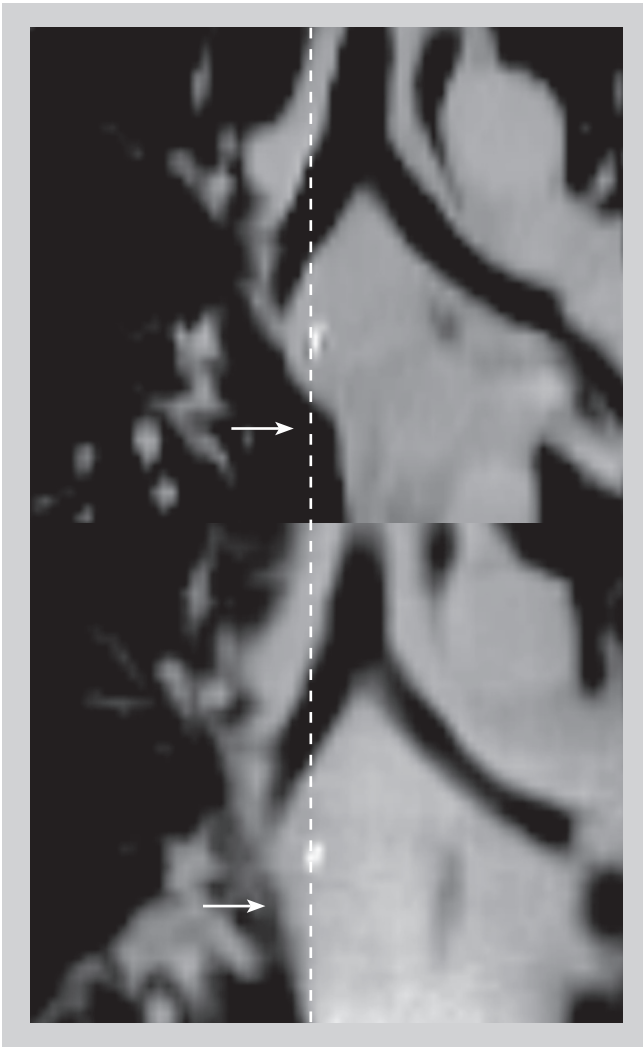


Figure 4. Coronal view of the planning CT scan and CBCT scan of the last fraction for the patient for which accurate local rigid soft tissue registration was not feasible due to substantial anatomical changes at the mediastinal-lung interface.

margins required to account for residual uncertainty of lymph node position following an online bony anatomy based correction protocol were 1.24 cm in this direction.

Respiratory motion was also largest in the CC direction but on average somewhat smaller than reported for the primary tumor (2). The amplitude variability over the course of treatment was equal or smaller than 1 mm. Relative to the amplitude obtained from the planning CT, somewhat larger differences were found. This is likely caused by the difference in imaging modalities. Where a 4D CT captures the motion of a single respiratory cycle, a 4D CBCT represents the average over many (30-60) respiratory cycles and therefore better captures the average respiratory behaviour of the patient.

In this study we evaluated the use of a carina based correction strategy to reduce the geometrical uncertainties of the lymph nodes as described in the study of Higgins et al.(15) and found a considerable reduction in the CC direction from 1.24 cm to 0.82 cm. Note however, that the clinical relevance of a carina based correction strategy depends on the differential motion between primary tumor and the carina. In this study, the number of patients was too low to evaluate this correlation taking the large variation in tumor location into account. Similarly, this study evaluates the lymph node base line shift irrespective of lymph node station. A larger patient group is required to evaluate if baseline variation and respiratory motion (variability) varies with lymph node station. Finally, note that the margins calculated in this study are based a margin recipe that was derived to determine margins for a single target. In case of multiple lymph nodes and tumor with limited correlation in their baseline variation, somewhat larger margins are required to obtain the same probability to cover all targets.

Lymph node motion is common and variable but the techniques of motion registration so far were not objectified during actual treatment and are subject of inter- and intra-observer variability due to a limited number of evaluated scans. Lymph node motion has been correlated to the motion of surrounding structures and the motion of surrogate references. These studies outlined mediastinal nodal stations 1–8, according to Naruke (16), with respectively 1 or 3 scans per patient evaluated (17, 18). Another study evaluated motion on 2 inhale and exhale controlled CT scans and compared displacement in three directions (19) or were correlated to changes in the carina position (20).

The current margins are based on estimates while with new techniques there is a better insight to be gained of true lymph node motion. For the primary lung tumors this has resulted in adaptive radiotherapy; frequently regression of shift have been observed and accounted for. For lymph nodes less variation and regression is expected. But resolving atelectasis or a regressing tumor can influence the lymph nodes position compared to the planning CT as well. Seven of the 14 nodes had average amplitude of over 0.5 cm with a maximum of 1.06 cm (SD 0.12 cm). With an average systematic error up to 0.34 cm in CC direction it is evident that there is more variability then anticipated in current protocols. So far, offline correction protocols were used to account for these set-up evaluations and eventual replanning. The margins after offline correction for this study would be up to 1.80 cm in CC direction.

Currently, online correction protocols are being used in our clinic, giving smaller residual error allowing the use of smaller margins. In the new protocol a tumor match, carina match and bone match will be performed to quantify the differential motion per patient and replan when required. This study shows that current lymph node margins of 12 mm are narrow for offline correction protocols.

REFERENCES

1. Borst GR, Sonke JJ, Betgen A, et al.: Kilo-voltage cone-beam computed tomography set-up measurements for lung cancer patients; first clinical results and comparison with electronic portal-imaging device. *Int J Radiat Oncol Biol Phys* 68:555-561, 2007
2. Sonke JJ, Lebesque J, van Herk M: Variability of four-dimensional computed tomography patient models. *Int J Radiat Oncol Biol Phys* 70:590-598, 2008
3. Henkelman RM, Mah K: How important is breathing in radiation therapy of the thorax? *Int J Radiat Oncol Biol Phys* 8:2005-2010, 1982
4. Graham MV, Purdy JA, Emami B, et al.: Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 45:323-329, 1999
5. Jenkins P, D'Amico K, Benstead K, et al.: Radiation pneumonitis following treatment of non-small-cell lung cancer with continuous hyperfractionated accelerated radiotherapy (CHART). *Int J Radiat Oncol Biol Phys* 56:360-366, 2003
6. Rancati T, Ceresoli GL, Gagliardi G, et al.: Factors predicting radiation pneumonitis in lung cancer patients: a retrospective study. *Radiother Oncol* 67:275-283, 2003
7. Seppenwoolde Y, Lebesque JV, de Jaeger K, et al.: Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. *Int J Radiat Oncol Biol Phys* 55:724-735, 2003
8. Tsujino K, Hirota S, Endo M, et al.: Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys* 55:110-115, 2003
9. Jaffray DA: Image-guided radiation therapy: from concept to practice. *Semin Radiat Oncol* 17:243-244, 2007
10. Lennon AM, Penman ID: Endoscopic ultrasound in cancer staging. *Br Med Bull* 84:81-98, 2007
11. Wolthaus JW, Schneider C, Sonke JJ, et al.: Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. *Int J Radiat Oncol Biol Phys* 65:1560-1571, 2006
12. van Herk M, Remeijer P, Rasch C, et al.: The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 47:1121-1135, 2000
13. Sonke JJ, Rossi M, Wolthaus J, et al.: Frameless stereotactic body radiotherapy for lung cancer using four-dimensional cone beam CT guidance. *Int J Radiat Oncol Biol Phys* 74:567-574, 2009
14. Witte MG, van der Geer J, Schneider C, et al.: The effects of target size and tissue density on the minimum margin required for random errors. *Med Phys* 31:3068-3079, 2004
15. Higgins J, Bezjak A, Franks K, et al.: Comparison of spine, carina, and tumor as registration landmarks for volumetric image-guided lung radiotherapy. *Int J Radiat*

Oncol Biol Phys 73:1404-1413, 2009

16. Naruke T, Suemasu K, Ishikawa S: Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J Thorac Cardiovasc Surg* 76:832-839, 1978
17. Bosmans G, van Baardwijk A, Dekker A, et al.: Time trends in nodal volumes and motion during radiotherapy for patients with stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 71:139-144, 2008
18. Pantarotto JR, Piet AH, Vincent A, et al.: Motion analysis of 100 mediastinal lymph nodes: potential pitfalls in treatment planning and adaptive strategies. *Int J Radiat Oncol Biol Phys* 74:1092-1099, 2009
19. Thomas JG, Kashani R, Balter JM, et al.: Intra and interfraction mediastinal nodal region motion: implications for internal target volume expansions. *Med Dosim* 34:133-139, 2009
20. Piet AH, Lagerwaard FJ, Kunst PW, et al.: Can mediastinal nodal mobility explain the low yield rates for transbronchial needle aspiration without real-time imaging? *Chest* 131:1783-1787, 2007