



Adaptive radiotherapy in lung

Adaptive radiotherapy for advanced lung cancer ensures target coverage and decreases lung dose



Ditte Sloth Møller^{a,*}, Marianne Ingerslev Holt^b, Markus Alber^c, Marie Tvilum^b, Azza Ahmed Khalil^b, Marianne Marquard Knap^b, Lone Hoffmann^a

^a Department of Medical Physics; ^b Department of Oncology, Aarhus University Hospital, Denmark; ^c Department of Radiation Oncology, Heidelberg University Hospital, Germany

ARTICLE INFO

Article history:

Received 4 March 2016

Received in revised form 16 August 2016

Accepted 29 August 2016

Available online 16 September 2016

Keywords:

IGRT

NSCLC

SCLC

Adaptive RT

Interfractional shifts

ABSTRACT

Background and purpose: Advanced lung cancer patients experience anatomical changes during radiotherapy. Uncorrected, these may lead to lower tumor dose, but can be corrected for by adaptive radiotherapy (ART).

Material and methods: Anatomical changes in 233 patients were monitored online on cone-beam CT-scans used for daily soft-tissue matching. If systematic changes above the pre-defined trigger criteria were observed, a new CT-scan, delineations, and treatment plan were made, restoring the intended dose distribution. Dose distributions with and without adaptation were compared. The first fifty ART patients were given two surveillance CT-scans during radiotherapy. These were used to evaluate delivered dose for patients without adaptation. The first fifty-two patients treated with ART were also compared with 52 pre-ART patients to evaluate the reduction in normal tissue doses.

Results: Sixty-three patients (27%) were adapted. Seventy-five per cent of all adaptations correctly adjusted for a decrease in tumor dose. Eighty-seven surveillance CT-scans were obtained for the first fifty patients and in only 2% of the cases, a decrease in tumor coverage ($\Delta V_{95\%CTV} > 1\%$) was observed. With ART we observed a significant decrease in lung dose (MLD reduced from 14.6 Gy to 12.6 Gy on average). **Conclusions:** Implementation of soft-tissue match combined with ART decreased the lung dose. The trigger criteria used correctly identified all but one (98%) of the patients requiring adaptation with a false positive rate of 20%.

© 2016 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 121 (2016) 32–38

Definitive chemo-radiation for advanced lung cancer struggles with poor local control rates [1] and potentially lethal toxicities, particularly pneumonitis [2,3]. Smaller treatment volumes are therefore desirable in order to decrease the lung dose and potentially the rate of pneumonitis. This may also increase the possibilities for dose escalation e.g. by dose painting, even though the benefit of dose escalation of non small cell lung cancer (NSCLC) above 66 Gy/33 Fractions (F) is debatable after the results of the RTOG 0617 trial [4].

A substantial fraction of the treated volume consists of safety margins for setup errors, which can be reduced by image-guided setup procedures. The transition from bone match to soft tissue match decreases the margins needed to account for interfractional baseline shifts [5–7]. However, it also makes the radiation plan more vulnerable to soft tissue changes and baseline shifts

in relative position of tumor and lymph nodes that are not explicitly accounted for by the margins.

Adaptive radiotherapy (ART) [8–10] adjusts the treatment plan to systematic changes observed during the course of RT, and restores the target dose in the case of e.g. large baseline shifts. Anatomical changes affecting the dosimetry, such as pleural effusion or atelectasis [11–13], are another trigger for ART, though not part of margin considerations. A special case is tumor shrinkage where adaptation of the treatment plan to the smaller tumor volume can lower the dose to organs at risk (OARs) [9,14]. However, this may also result in under dosage of microscopic disease in the periphery of the target. Alternatively, isotoxic increase of the target dose may be achieved [15].

Appearance or disappearance of atelectasis is one of the main reasons for adaptation in lung cancer patients. Unfortunately, there is no common time trend in these changes [11] and some kind of surveillance during the course of RT is needed [9,12]. Daily cone beam CT (CBCT) for patient setup can be used to trigger adaptation in a clinical setting [11,13,16]. Other studies used 3D portal dosimetry for the clinical evaluation of dosimetric changes [17].

* Corresponding author at: Aarhus University Hospital, Department of Medical Physics, Noerrebrogade 44, Building 5J, 2. Floor, 8000 Aarhus C, Denmark.

E-mail address: dittmoel@rm.dk (D.S. Møller).

In this prospective study, ART relies on daily online evaluation of pre-treatment CBCTs with geometric criteria to trigger adaptation. We demonstrate the efficacy of the trigger criteria and the dosimetric advantages of this adaptive strategy in terms of reduced dose to OARs and persistent target coverage throughout the treatment course. In this study, we do not consider adaptation to shrinking targets which remain within the original treatment field.

Material and methods

Patient characteristics and treatment planning

Two-hundred and thirty-three consecutive lung cancer patients were included in the study (173 patients with NSCLC and 60 with SCLC). The stage distribution was 5 patients in IA, 4 in IB, 16 in IIA, 21 in IIB, 104 in IIIA, 73 in IIIB and 10 in IV. Overall, 76% of the patients had stage III disease. The patients with stage IV had oligometastatic disease. Ten patients received postoperative irradiation. The prescribed dose was 50 Gy/25 fractions (fx) (11 patients), 60 Gy/30 fx (44 patients), 66 Gy/33 fx (123 patients) or 45 Gy/30 fx (55 patients). Standard chemo therapy for NSCLC was concomitant cis/carbo-platinum and vinorelbine (three cycles). For SCLC concomitant cis/carbo-platinum and etoposide (four cycles).

All patients were delineated on a combined free-breathing ^{18}F -FDG-PET/4D-CT scan with i.v. contrast. The internal gross tumor volume (iGTV) was delineated on the mid-ventilation phase of the 4D-CT as a sum of all GTV phases to account for respiratory motion [18]. The PET scan was used to guide the delineation. The clinical target volume (CTV) was created by adding a 5 mm expansion cropped with respect to bones and large blood vessels. An IMRT plan with 5–10 fields was optimized for each patient using the AAA algorithm (Varian Medical Systems). The target was covered by a homogeneous dose distribution (95–107%) except in five patients where dose escalation of the GTV was performed.

Daily imaging, PTV margin and adaptation

A 3D-CBCT scan was acquired for all patients before each fraction with an acquisition time of approximately 1 min. This resulted in a respiratory weighted tumor position used for set-up. The patients were set up according to the position of the primary tumor except in patients without primary tumor, where the lymph-node target was used. After set-up, the radiation therapists (RTTs) evaluated the following trigger criteria (see Fig. 1):

- the position of the tumor with a 2 mm tolerance.
- the position of lymph nodes via designated surrogate structures described in [16] with a 5 mm tolerance.
- the position of the thoracic vertebra with either a 5 mm or a 10 mm tolerance depending on the dose plan.
- changes in lung density (atelectasis, pleural effusion or pneumonia) defined as occurring or not occurring.
- body contour changes with a 15 mm tolerance.
- changes in the mediastinum including heart with a 10 mm tolerance.

If a tolerance was exceeded or a change in lung density appeared for three consecutive fractions, a medical physicist would evaluate if a re-scan and a plan adaptation were needed. Geometrically, the physicist evaluated if the deviations observed were correct and systematically above the tolerance. Dosimetric changes were evaluated as described in [11].

The CTV-PTV margins (anterior-posterior, left-right, superior-inferior) were 4, 4, 5 mm and 9, 9, 10 mm for the tumors and the lymph nodes, respectively. All systematic (Σ) and random errors (σ) were quantified in the clinical setting at Aarhus University

Hospital. Part of the margins was inter-fractional base-line shifts observable on CBCT. These errors were $\Sigma = 0$ and $\sigma = 0$ for the primary tumor and $\Sigma = 1.2$ mm and $\sigma = 1.1$ mm for the lymph nodes [16]. Thus, the tumor margin can be tight, but due to relative motion of tumor and lymph nodes, a larger margin is required for the latter. The margins furthermore included errors from delineation uncertainties ($\Sigma = 1$ mm), intra-fractional baseline shifts, inter-fractional target deformations, deviations in MLC, couch, and CBCT isocenter position, CT-distortion and partial volume effects. In addition, the margins for the lymph nodes included uncertainties originating from the use of surrogate structures for the evaluation [16]. Without daily soft-tissue image guidance, correcting for inter-fractional errors these margins would be too tight.

A new 4D-CTscan (re-CT) was acquired, if decision was made to adapt the existing treatment plan. Target and OARs were delineated by an experienced radiation oncologist based on both a rigid and a deformable transfer of the initial delineations. The treatment plan was not adapted to shrinking tumors and the absolute CTV size was attempted unchanged. In the case of large deformations or shrinkage in the mediastinum where anatomical borders such as bones and vessels were respected, this was not possible. Finally, a new treatment plan was made by re-optimization.

Evaluating the effect of adaptation

For the subgroup of patients re-planned due to ART, the dose distributions of the re-plans were compared to a recalculation of the original treatment plan on the re-CT. The original treatment plan was transferred to the re-CT through a 4D rigid registration (including yaw couch rotation) based on the primary GTV mimicking the clinical set-up strategy. The volume covered by 95% of the prescribed dose (V95%) was used as a measure of the CTV and PTV coverage. The clinical criterion for adaptation was defined as a decrease in coverage of the CTV by more than 1% or the PTV by more than 3%. The geometric criteria used for evaluation of tumor and lymph nodes were chosen to achieve this goal. Since the inter-fractional shifts observed on the daily CBCTs and the re-CTs constitute only a minor part of the CTV-PTV margin, under dosage of the PTV may potentially lead to under dosage of the CTV.

Surveillance scan

The first 50 patients treated in the ART protocol were followed with two extra surveillance 4D-CT scans (s-CT) at fractions 10 and 20, approximately. These scans were used to investigate if patients that were not re-planned could have had benefit from adaptation. The existing treatment plan at the time of the s-CT scan was recalculated on the s-CT and the dose distribution was compared to that of the treatment plan. Thus, the surveillance scans were meant to assess the false negative rate of the adaptation trigger criterion.

Clinical control group

The dosimetric parameters of the first 52 ART patients were compared to 52 pre-ART patients. The two groups are described in detail in [19] and differed only by margins and set-up strategy and not by clinical parameters. For the pre-ART patients, the GTV was delineated on the midventilation-scan of the 4D-CT and the CTV was expanded similar to the ART group. Standard respiratory internal target volume (ITV) margins (5, 5, 10 mm) and PTV margins (5, 5, 8 mm) were added. The patients had a daily CBCT and were set-up on the thoracic vertebra with a 5 mm tolerance. In the ART group, 12 patients had their treatment plans adapted. The two groups were compared in terms of target coverage and dose to the lung, heart and esophagus using a 1-sided student's *t*-test. A *p*-value of 0.05 was considered significant.

Results

Surveillance scan

Fifty patients had one or two surveillance scans performed. In total, 87 scans were obtained. Five scans were excluded, as the s-CT deviated from the CBCT obtained at the identical fraction. The deviation was due to problems with irreproducible fixation or large systematic errors in diaphragm position on the s-CT.

In the remaining 82 s-CTs, the CTV and PTV coverage was within the clinical criteria in 98% of the scans. In one patient (2% of the scans), both s-CT scans showed a decrease of 4% in V95% of both CTV and PTV due to deformation of the primary tumor not visible on CBCT. This shows that the adaptation trigger criteria were sensitive enough to ensure target coverage in all but one case.

Adaptation

In total, 79 adaptations were performed. Sixty-three of 233 patients (27%) were re-planned once due to the adaptive strategy. Ten patients were re-planned twice and three patients were re-planned three times.

Fifty-nine (75%) adaptations corrected a decrease in target coverage or an over dosage of the spinal cord (see example in Fig. 2a. For the remaining 20 adaptations, no gain was obtained. Four adaptations were due to changes in atelectasis close to the primary tumor where distinction between tumor and atelectic tissue was not visible. This made the online match evaluation impossible

and these four adaptations were justified in order to secure the online match. After adaptation the distinction was still not visible on CBCT, but the similarity between CBCT and CT was better, aiding the online evaluation. Sixteen adaptations were not justifiable, so the false positive rate was 20%. These adaptations were ineffective because target shrinkage or the particular nature of the dose distributions counterbalanced the geometric shifts that triggered adaptation (see Fig. 2b), indicating a potential efficiency gain of a dose-based trigger criterion, where the decision e.g. could be based on transferring contours to and recalculating dose on the daily CBCT scans. The 20 adaptations that did not correct for a decrease in target coverage were excluded from further analysis.

The 59 justifiable adapted treatment plans were grouped according to the cause for adaptation, see Table 1. If re-planning was performed to avoid a risk of target miss, three sub groups could be distinguished: under dosage of either the primary tumor (T), the lymph node (N) or both (T + N). For each group the average decrease in coverage of PTV and CTV is shown in Table 1. The decrease in coverage for all individual patients is shown in Fig. 3 for groups with more than 1 patient. In one patient, re-planning was solely due to a large shift of the vertebral column. In this patient, the dose to a volume of 0.05 cm³ receiving the highest dose ($D_{0.05\text{cm}^3}$), increased by 2.5 Gy to 46 Gy (constraint 45 Gy).

For some patients, the anatomical changes during RT also affected the dose to OAR. In the cohort of 79 adaptations, seven patients would have had $D_{0.05\text{cm}^3}$ above 45 Gy for the spinal cord without adaptation. In eight patients, $D_{10\text{cm}^3}$ to the heart was larger than 50 Gy in the primary plan and changed by more than 5 Gy on

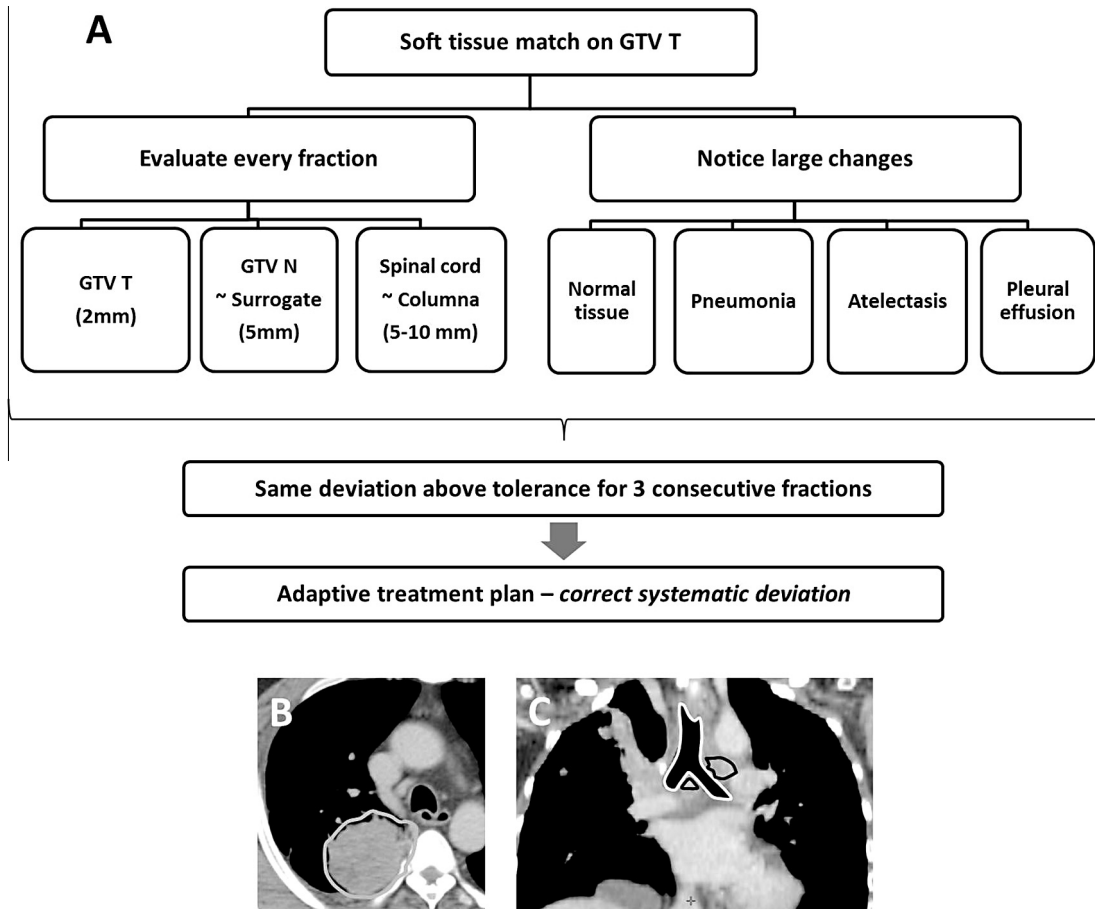


Fig. 1. (A) Flowchart for online adaptive evaluation. (B) Evaluation of primary tumor. A structure (gray) consisting of the GTV-T with a 2 mm isotropic margin is delineated and the primary tumor has to stay within this structure at the daily treatments. (C) The lymph nodes (black) are not easily visible on CBCT and are therefore evaluated via surrogate structures (white) with a 5 mm tolerance.

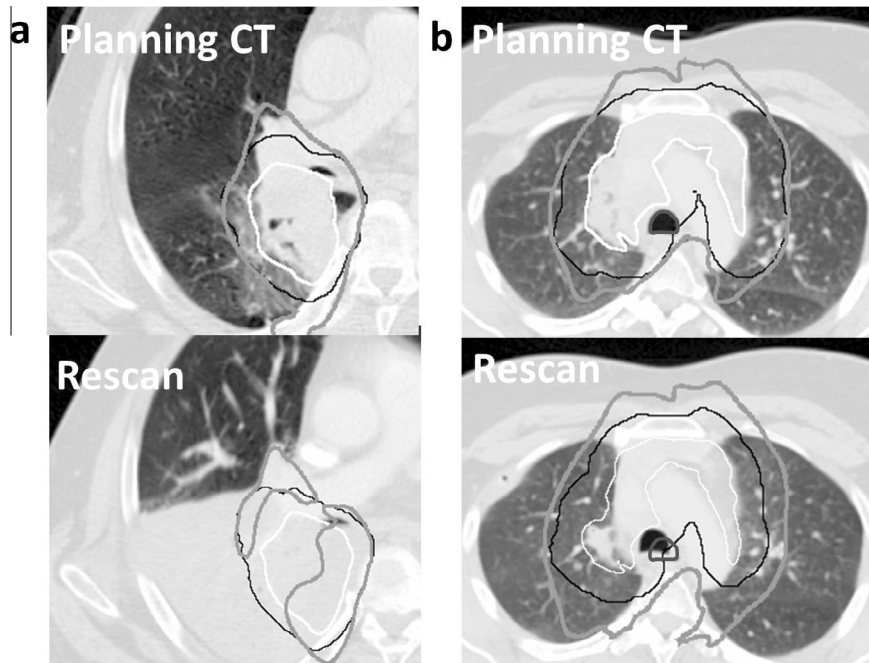


Fig. 2. Comparison of targets and dose coverage for two patient examples. Tumor or lymph node GTV (white), PTV (black) and 95% isodose line (gray) are shown for the plan on the planning CT in the upper panel and re-delineations and recalculation of the plan on the re-scan in the lower panel. a) shows a patient where an atelectasis occurs during the course and under dosage of the target is seen. b) shows a patient where a deformation and shrinkage of the mediastinum gives a deviation on the surrogate (dark gray), but no under dosage of the target is seen. The surrogate is shown on the re-scan as a rigid transfer to illustrate the deviation, whereas GTV, PTV are re-delineations and the isodose line is recalculated.

Table 1

Under dosage of PTV and CTV for different groups of adaptations.

Reason	Consequence	Patient number	Average decrease in V95% for PTV [%]	Average decrease in V95% for CTV [%]	Median fx number
Target	Underdosage of N [#]	12	9.1	1.2	15
	Underdosage of T [*]	16	10.3	1.9	14
	Underdosage of T + N	13	12.4	3.0	12
Atelectasis	Underdosage of T + N	16	14.0	7.5	13
Pleural effusion	Underdosage of T + N	1	15.4	9.6	12
Diaphragm	Underdosage of T + N	1	5.2	3.0	12

^{*} Under dosage of primary target (PTV-T and CTV-T) is shown.

[#] Under dosage of lymph node target (PTV-N and CTV-N) is shown. The last column shows the median fraction number when a re-plan starts for each group.

the re-scan or the adapted plan on the re-scan, i.e. the re-plan. In 4 of these patients, the heart dose increased when the plan was recalculated on the re-scan, and the dose was restored by adaptation in 3 patients, while the increased value was persistent in the remainder. In 4 patients, the heart dose was unchanged when the plan was recalculated on the re-scan, but since the tumor or lymph nodes were closer to the heart on the re-scan the tumor was under dosed. Restoring the target dose by re-planning increased the heart dose.

Treatment adaptation was performed at any time point during the radiotherapy course. The median times for onset of the adapted treatment plans are shown in Table 1. The upper panel in Fig. 4 shows a distribution of the onset of the adapted treatment plans for the 59 correctly adapted patients divided into the first adaptation (48 patients), the second adaptation (9 patients), and the third adaptation (2 patients). The lower panel focuses on the first adaptation and shows a plot of the cumulative number of adaptations during the course of RT. A logistic fit to the latter yields $N(t) = N_{\text{tot}} / (1 + \exp(3.0 - 0.27 * t))$, where $N_{\text{tot}} = 48$ is the total number of primary adaptations and N the number of primary adaptations performed at fraction t . For patients eventually requiring adaptation, the odds for such an event grow daily by a factor $\exp(0.27) = 1.31$. For clinics implementing adaptive radiotherapy, the plot

shows the clinical workload due to adaptation through the treatment course.

Comparison to clinical control group

The implementation of online primary tumor set-up and ART made it possible to decrease the CTV-PTV margins and comparison of the first 52 ART patients with 52 pre-ART patients showed similar GTV-sizes but a significant decrease in PTV volumes. As shown in Table 2, doses to the lung, heart and esophagus decreased due to the decreased margins. However, only the decrease in lung dose was statistically significant with a 0.05 significance level. As shown in [19] this decrease in lung dose also leads to a decrease in severe radiation pneumonitis.

Discussion

The study evaluates the dosimetric results of 233 patients treated prospectively with adaptive radiotherapy. Geometric criteria triggering adaptation were applied daily and systematically by RTTs and decision for re-planning was made accordingly. Ninety-eight percent of the patients requiring adaptation were detected by the ART strategy and 75% of the patients selected for re-

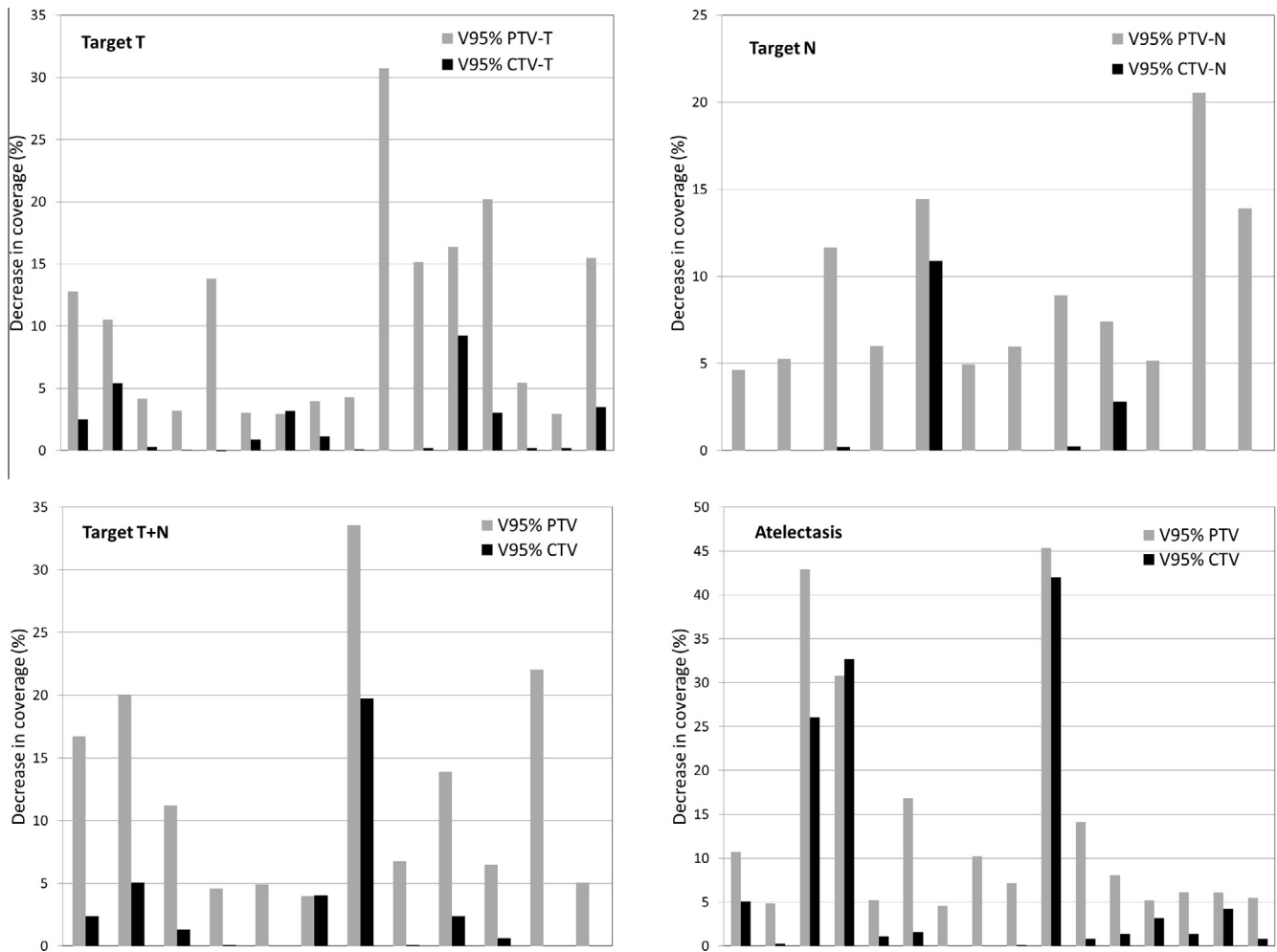


Fig. 3. Decrease in V95% of PTVs and CTVs for the four largest groups of adaptations.

planning truly benefit from the re-planning. Twenty-seven percent of all patients were re-planned, including a false-positive group. This need for adaptation in a subgroup of patients is also found in other studies [12,13,20,21]. However, the adaptation rate differs depending on the geometric and dosimetric criteria applied. Our dosimetric evaluation found 59 justifiable adaptations with the strict clinical criteria applied. Softening the criteria, and accepting i.e. 5% under dosage of the CTV and no PTV criteria, results in only seven adaptations being needed. In our ART strategy, narrow margins combined with strict clinical criteria have been shown to improve local control [19].

Margins in radiotherapy are typically designed to assure target coverage for i.e. 90% of the patients [22] taking into account different systematic and random errors. The radiation oncologist either accepts under dosage of 10% of the patients, accepts very large margins with increased toxicity for all patients, or uses ART to track and re-plan those patients. The match between the margin and ART-strategy is therefore essential. In a group of 50 patients with surveillance scans independent of the daily imaging, we found a rate of false negatives (patients not adapted although necessary) of only 2%. This shows that our margins are consistent with the geometrical triggers used for the adaptive strategy. In addition, all density changes (atelectasis, pleural effusion etc.) and associated dosimetric changes would not generically be accounted for by margins. The decrease in coverage of the CTV and PTV depends on the nature of the anatomical changes. Geometric shifts mainly affect the PTV coverage, while the CTV coverage decreases when

deformations and density changes are present. The study therefore shows no common correlation between the CTV and PTV coverage.

Our results show a false positive rate of 20% because the geometric criterion triggering adaptation is not absolutely in concordance with the dosimetric consequence seen. After analysis of the first fifty patients the problem with false positives was seen and new training was given to the physicists, which improved the rate. In first 123 patients treated before the new instructions 11 false positives were seen, in the last 110 patients treated after improved instructions only 5 false positives were seen. The rate could possibly be improved further by relaxing the geometric criteria accepting the risk of a lower true positive rate. Nevertheless, the discrepancy between the geometric trigger criteria and the results of re-planning will not disappear without a real dose-based trigger criterion. This will probably be possible in the future with improvement of deformable image registration [23] and dose calculation on CBCT [24].

Atelectasis in particular, is responsible for a large number of adaptations (9% of all patients in this study), 12% in [11] and 10% in [17]. In this study, atelectasis and other dosimetric changes were found by visual inspection of the daily CBCTs. As shown in [17] atelectasis can be found with a 76% success rate by the use of 3D portal dosimetry, compared to a 98% success rate with the daily visual inspection in this study.

Adaptations also change the doses to OAR. In this study we e.g. report on seven patients where the protection of the spinal cord was assured through adaptation. In the case of dose escalation, the need

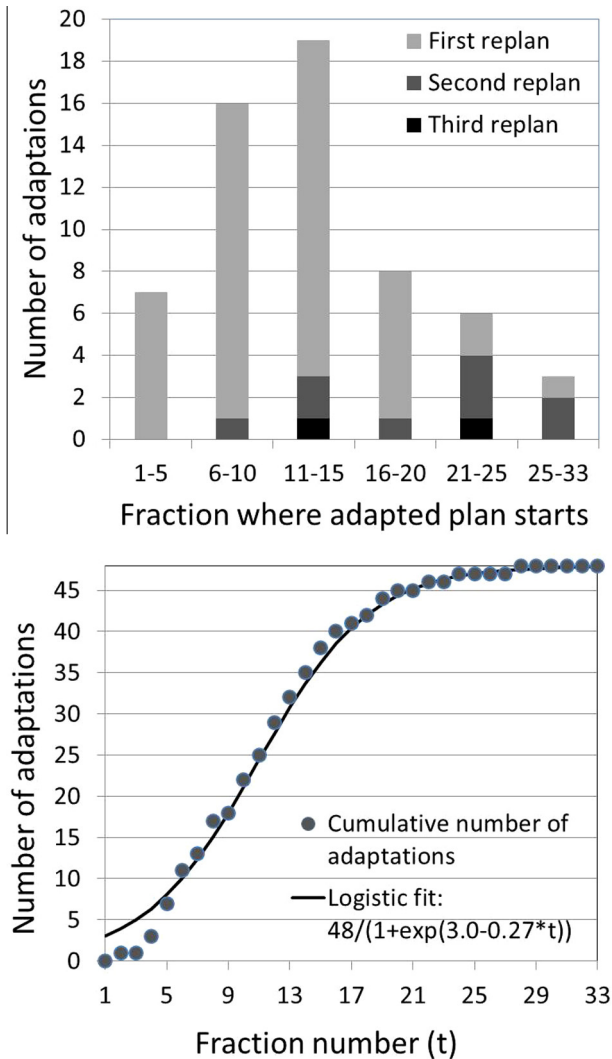


Fig. 4. Upper panel: Distribution of the onset of the first, second and third adapted plans. Lower panel: Cumulative number of primary adaptations as function of the fraction number with a logistic fit.

Table 2
Dosimetric parameters of the ART and pre-ART group.

Patients (n)	ART (n = 52)	Pre-ART (n = 52)	p-value (1 sided)
NSCLC/SCLC	38/14	38/14	
GTV size	98.3 cm ³	107.5 cm ³	0.39
PTV size	400 cm ³	599 cm ³	<0.001
Dose NSCLC	64.9 Gy	64.0 Gy	0.14
Dose SCLC	45.0 Gy	45.1 Gy	0.17
MLD	12.6 Gy	14.4 Gy	0.02
V20 – lung	22.6%	25.7%	0.03
V5 – lung	45.3%	49.6%	0.04
MHD	8.0 Gy	10.0 Gy	0.08
V20 Heart	13.1%	17.0%	0.10
V45 Esophagus	15.7%	20.6%	0.07

for adaptation due to high doses to OARs is required more frequently [25].

In concordance with the observations in [11–12,17] and as shown in Fig. 4, adaptations are performed and needed at different times during treatment and frequent surveillance is thus important. Adaptations in the last part of the treatment course should only be performed when large changes occur, as the overall dosimetric benefit for the whole treatment is otherwise minimal.

ART requires re-delineation of the tumor. In this study, all tumors were delineated by an experienced radiation oncologist, based on both deformable and rigid transfer of the tumor delineation. This additional delineation introduces uncertainty [26,27]. In this study, we have chosen not to adapt to shrinking tumors, but it can be difficult to maintain the original CTV-size in the delineation process, if substantial tumor shrinkage has occurred.

The ART strategy was implemented as daily routine in our clinic and there are no practical limitations for implementation at other institutions. It was implemented with well-defined criteria making the decision independent of the decision maker. The implementation enabled a safe margin reduction resulting in reduced lung dose and as shown in [19] a reduced risk of radiation pneumonitis.

In conclusion, we have implemented an adaptive strategy for locally advanced lung cancer patients and shown that the strategy ensures target coverage and the majority of the adaptations were dosimetrically beneficial. Comparison with a clinical control group shows that the safe margin reduction made possible by soft tissue match and ART significantly reduces the lung dose.

Conflict of interest statement

None.

Acknowledgements

This research was supported by grant no. R124-A7821 from the Danish Cancer Society.

References

- [1] Auperin A, Le PC, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181–90.
- [2] Khalil AA, Hoffmann L, Møller DS, Farr KP, Knap MM. New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy. *Acta Oncol* 2015;54:1343–9.
- [3] Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76:S70–6.
- [4] Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187–99.
- [5] Knap MM, Hoffmann L, Nordsmark M, Vestergaard A. Daily cone-beam computed tomography used to determine tumour shrinkage and localisation in lung cancer patients. *Acta Oncol* 2010;49:1077–84.
- [6] Juhler-Nøttrup T, Korreman SS, Pedersen AN, et al. Interfractional changes in tumour volume and position during entire radiotherapy courses for lung cancer with respiratory gating and image guidance. *Acta Oncol* 2008;47:1406–13.
- [7] Yeung AR, Li JG, Shi W, et al. Tumor localization using cone-beam CT reduces setup margins in conventionally fractionated radiotherapy for lung tumors. *Int J Radiat Oncol Biol Phys* 2009;74:1100–7.
- [8] Yan D, Vicini F, Wong J, Martinez A. Adaptive radiation therapy. *Phys Med Biol* 1997;42:123–32.
- [9] Sonke JJ, Belderbos J. Adaptive radiotherapy for lung cancer. *Semin Radiat Oncol* 2010;20:94–106.
- [10] Gomez DR, Chang JY. Adaptive radiation for lung cancer. *J Oncol* 2011;2011.
- [11] Møller DS, Khalil AA, Knap MM, et al. Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. *Radiother Oncol* 2014;110:517–22.
- [12] Britton KR, Starkschall G, Liu H, et al. Consequences of anatomic changes and respiratory motion on radiation dose distributions in conformal radiotherapy for locally advanced non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;73:94–102.
- [13] Kwint M, Conijn S, Schaake E, et al. Intra thoracic anatomical changes in lung cancer patients during the course of radiotherapy. *Radiother Oncol* 2014;113:392–7.
- [14] Berkovic P, Paelinck L, Lievens Y, et al. Adaptive radiotherapy for locally advanced non-small cell lung cancer, can we predict when and for whom? *Acta Oncol* 2015;54:1438–44.
- [15] Guckenberger M, Richter A, Wilbert J, Flentje M, Partridge M. Adaptive radiotherapy for locally advanced non-small-cell lung cancer does not

- underdose the microscopic disease and has the potential to increase tumor control. *Int J Radiat Oncol Biol Phys* 2011;81:e275–82.
- [16] Hoffmann L, Holt MI, Knap MM, Khalil AA, Møller DS. Anatomical landmarks accurately determine interfractional lymph node shifts during radiotherapy of lung cancer patients. *Radiother Oncol* 2015;116:64–9.
- [17] Persoon LC, Podesta M, Hoffmann L, Sanizadeh A, Schyns LE, de Ruiter BM, et al. Is integrated transit planar portal dosimetry able to detect geometric changes in lung cancer patients treated with volumetric modulated arc therapy? *Acta Oncol* 2015;54:1501–7.
- [18] Chang JY, Dong L, Liu H, et al. Image-guided radiation therapy for non-small cell lung cancer. *J Thorac Oncol* 2008;3:177–86.
- [19] Tvilum M, Khalil AA, Møller DS, Hoffmann L, Knap MM. Clinical outcome of image-guided adaptive radiotherapy in the treatment of lung cancer patients. *Acta Oncol* 2015;54:1430–7.
- [20] Schmidt ML, Hoffmann L, Kandi M, Møller DS, Poulsen PR. Dosimetric impact of respiratory motion, interfraction baseline shifts, and anatomical changes in radiotherapy of non-small cell lung cancer. *Acta Oncol* 2013;52:1490–6.
- [21] Weiss E, Robertson SP, Mukhopadhyay N, Hugo GD. Tumor, lymph node, and lymph node-to-tumor displacements over a radiotherapy series: analysis of interfraction and intrafraction variations using active breathing control (ABC) in lung cancer. *Int J Radiat Oncol Biol Phys* 2012;82:e639–45.
- [22] van Herk M. Errors and margins in radiotherapy. *Semin Radiat Oncol* 2004;14:52–64.
- [23] Hardcastle N, van Elmpt W, De Ruysscher D, Bzdusek K, Tomé WA. Accuracy of deformable image registration for contour propagation in adaptive lung radiotherapy. *Radiat Oncol* 2013;8:243.
- [24] Fotina I, Hopfgartner J, Stock M, Steininger T, Lütgendorf-Caucig C, Georg D. Feasibility of CBCT-based dose calculation: comparative analysis of HU adjustment techniques. *Radiother Oncol* 2012;104:249–56.
- [25] Hoffmann L, Knap MM, Khalil AA, Møller DS. Dose escalation in lung cancer patients, the dosimetric implications of inter-fractional change. *Radiother Oncol* 2016;119:S168–9.
- [26] Ellegaard MB, Knap MM, Hoffmann L. Inter-tester reproducibility of tumour change in small cell lung cancer patients undergoing chemoradiotherapy. *Acta Oncol* 2013;52:1520–5.
- [27] Speight R, Sykes J, Lindsay R, Franks K, Thwaites D. The evaluation of a deformable image registration segmentation technique for semi-automating internal target volume (ITV) production from 4DCT images of lung stereotactic body radiotherapy (SBRT) patients. *Radiother Oncol* 2011;98:277–83.