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Adaptive radiotherapy in lung

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

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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 ($\Delta V95\%_{CTV} > 1\%$) 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%.

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].

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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 vinorelbin (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.