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Improving radiation dose delivery for moving targets using image guidance

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Dose-guided radiotherapy: The potential benefit of on-line dose recalculation for stereotactic lung irradiation in patients with Non-Small Cell Lung Cancer

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7.1 Abstract

Purpose: To determine whether dose-guided radiotherapy (DGRT), i.e. on-line recalculation and evaluation of the actual dose distribution can improve the decision making for lung cancer patients treated with stereotactic body radiotherapy (SBRT).

Methods and Materials: For this study 108 cone-beam CT (CBCT) scans of 10 non-small cell lung cancer (NSCLC) patients treated with SBRT were analyzed retrospectively. The treatment plans were recalculated on the CBCT scans. $V_{100\%}$ of the internal target volume (ITV) and D_{\max} of the organs at risk (OARs) were analyzed. Results from the recalculated data are compared to dose estimates for target and OARs by superposition of the originally planned dose distribution on CBCT geometry: i.e. the original dose distribution is assumed to be spatially invariant.

Results: Before position correction was applied $V_{100\%}$ of the ITV was 100% in 65% of the cases when an ITV-PTV margin of 5mm was used and 52% of the cases when a margin of 3mm was used. After position correction, the difference of D_{\max} in the OARs with respect to the treatment plan was within 5% in the majority of the cases. When the dose was not recalculated, but estimated based on assuming an invariant dose distribution, clinically relevant errors occurred both in the ITV and the OARs.

Conclusion: DGRT can be used to determine the actual dose in OARs when the target has moved with respect to the OARs. When the workflow is optimized for speed, it can be used to prevent unnecessary position corrections. Estimating the dose by assuming an invariant dose instead of recalculation of the dose gives clinically relevant errors.

7.2 Introduction

Stereotactic body radiotherapy (SBRT) aims at delivering a high biologically effective dose in a small number of treatment fractions. SBRT is often used in patients with stage I/II non-small cell lung cancer (NSCLC) who are unfit or unwilling to undergo surgery. Several studies have reported local control rates above 85% [89-91]. A major problem in SBRT for lung tumors is the interfraction variation in the time-averaged tumor position relative to the bony anatomy: the baseline shift [34] (figure 7.1a). The interfraction variation of the tumor position is corrected by adapting the patient position, but this may result in a higher dose in an organ at risk (OAR). To prevent overdosage to OARs, margins are drawn around the OARs to create a planning organ at risk volume (PRV).

In some cases the displacement of the tumor with respect to an OAR exceeds the size of the safety margin. Currently there is no clear protocol for such cases. Moreover, weight loss or a change in patient position that cannot be corrected can affect the dose distribution as a whole (figure 7.1b). When the dose distribution in the current situation can be evaluated on-line, an objective and well-considered decision can be made about how to proceed.

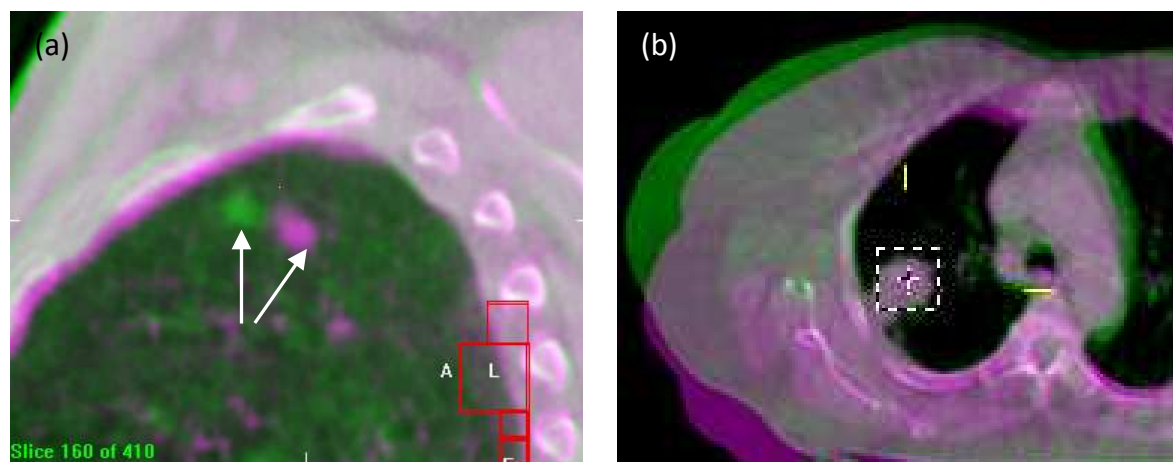


Figure 7.1: Two cases where an on-line dose calculation would be helpful. The purple scan represents the planning CT and the green scan represents the CBCT. (a) The tumor has moved with respect to the bony anatomy. When position correction is applied the dose in the OARs may be different from the treatment plan. (b) The shape of the patient has changed, which may cause a change in the dose distribution.

The goal of this study is to investigate the potential benefits of dose-guided radiotherapy (DGRT), i.e. on-line recalculation and evaluation of the dose distribution using a (near)

real-time image of the patient anatomy. This is done by retrospectively recalculating the dose distribution on the CBCT scans of ten NSCLC patients treated with SBRT .

7.3 *Methods and Materials*

7.3.1 **Patients**

Ten patients treated in our department with SBRT in the period October 2009 – May 2010 were included in this study. Planning CTs were acquired with a GE Lightspeed RT16 scanner (General Electric Healthcare, Waukesha, WI, USA) with the patient in supine position. The patients were lying on a polyurethane foam support cushion (Accessories RadioTherapy, Eindhoven, The Netherlands). The patient's head and arms were positioned on a Posirest-2 (Civco, Kalona, IA, USA).

7.3.2 **Target definition and treatment planning**

The internal target volume (ITV) was delineated on a slow CT scan and a PET-CT was used to guide the delineation. An ITV-planning target volume (PTV) margin of 5 mm was used, according to our clinical protocol. For comparison, a second plan was made using an ITV-PTV margin of 3 mm, because Hurkmans *et al.* recommended using a margin of 3-5 mm [92]. The OARs (spinal cord, oesophagus, heart and the trachea) were also defined as recommended [92]. An OAR-PRV margin of 10 mm was used. Note that this PRV margin was not used in the traditional way, i.e. to compensate for movement of the OAR itself, but to compensate for a possible baseline shift of the target with respect to the OARs.

The treatment plans and the recalculations on CBCT were made with Oncentra v4.0 (Nucletron B.V., Veenendaal, The Netherlands), using the collapsed cone algorithm [80]. Each plan consisted of 12-15 beams of 6 MV, which were non-coplanar. The beam angles were optimized to avoid the critical structures as much as possible. The prescribed dose was either 3x18 Gy (three patients) or 5x11 Gy (seven patients). The requirements of the treatment plan were that 95% of the PTV received at least the prescribed dose and 100% of the ITV received 100% of the prescribed dose. The constraints for the OARs depended on the fractionation scheme, as described in the recommendations of Hurkmans *et al* [92]. For the 3x18 Gy scheme the maximum doses were: 18 Gy to the spinal cord, 24 Gy to the esophagus and the heart and 30 Gy to the trachea. For the 5x11 Gy scheme the maximum doses were: 25 Gy to the spinal cord, 27 Gy to the esophagus and the heart and 32 Gy to the trachea.

7.3.3 CBCT scans

Before treatment a CBCT was made using the Synergy system (Elekta, Crawley, United Kingdom) and registered with XVI release 3.5 (Elekta, Crawley, United Kingdom). All CBCT scans were made using the same protocol: M20 collimator, 360° scan, 120 kV and a bow-tie filter [93]. The CBCT and planning CT scans were registered based on a grey value match of a volume that contained the tumor and a small part of the surrounding tissue. The rotations were converted into translations with the correction reference point in the center of the ITV.

The match results of the first CBCT of each fraction were executed without a threshold. After execution of the required correction, a new CBCT was made for verification. If the vector length of the registration result was smaller than 3 mm in the verification scan, the radiation was started. Otherwise a second correction was executed and a new CBCT scan was made. When the treatment was halfway, another CBCT was made to check whether the patient had moved. If the registration result exceeded the threshold of 3 mm, the position of the patient was corrected and another CBCT scan was made to verify this correction.

In this study only combinations of scans made before and after application of a correction were considered. Hence, the scans that were made halfway during treatment were only taken into account if the registration result exceeded the threshold. 108 CBCT scans were used for this study: 54 before and 54 after applying a position correction. 82 scans were taken at the start of the treatment and 26 halfway.

The delineated structures were copied onto the CBCT scan from the planning CT scan with the target shifted according to the tumor registration and the OARs shifted according to a bone match. The body contour was not copied, but automatically delineated on the CBCT scans [94].

Copying the OARs from the planning CT and shifting them with the bone match is an approximation of the position of those structures. For the spinal cord, this approximation is obviously accurate. For the esophagus and the trachea there might be a deviation with respect to the real position. However, delineation of the structures is time consuming and therefore unrealistic for the purpose of DGRT. Moreover, the poor soft-tissue contrast of the CBCT is likely to cause delineation errors. To give an indication of the uncertainty of the dose in those organs, we studied a worst-case scenario. We selected for each patient the scan of the first fraction, after correction. We moved the esophagus or the trachea,

whichever was closest to the target, 5 mm towards the target. The difference of the maximum dose of the moved and the original structure is reported.

7.3.4 Dose calculation

The CBCTs were exported from XVI with adapted DICOM export settings, i.e. the export parameter RescaleIntercept in the configuration file sri.ini was changed to -1024 in order to give the grey values of the CBCT the same range as Hounsfield units. A preliminary study has demonstrated that using these export settings and a standard CT HU-density table yielded a reliable dose distribution for CBCT scans made with the Elekta Synergy System. In this study dose distributions of several plans were calculated on the CBCT of a thorax phantom and this was compared to the dose distribution on CT. This study has shown that the number of voxels that fail the γ -analysis with a 3%/3mm criterion was less than 1% and the accuracy of the average dose in the target was also within 1%.

Recalculation of the treatment plans on CBCT is compared to an estimation of the dose in the target and the OARs based on superposition of the original planned dose distribution on CBCT geometry. In this approximation the dose was assumed to be spatially invariant.

7.3.5 Analysis

We compared the volume of the ITV that received 100% of the prescribed dose ($V_{100\%}$) of the recalculated dose distribution with $V_{100\%}$ of the original plan. In the original treatment plans this volume is 100%, i.e. 100% of the volume receives 100% of the prescribed dose.

$V_{100\%}$ was correlated with the vector of the match result R_{match} in order to determine the relation between the dose difference and the set-up error.

$$R_{\text{match}} = \sqrt{M_{\text{LR}}^2 + M_{\text{CC}}^2 + M_{\text{DV}}^2}, \quad (7.1)$$

where M_{LR} , M_{CC} and M_{DV} were the match results in the left-right, craniocaudal and dorsoventral direction, respectively.

For the OARs the difference of the maximum dose on the CBCT and on the planning CT was analysed. The reported difference is the relative error with respect to the prescribed dose.

$$\Delta D_{\text{max}} (\%) = \frac{D_{\text{max,CBCT}} - D_{\text{max,plan}}}{\text{PD}} \times 100, \quad (7.2)$$

Where ΔD_{\max} is the relative difference of the maximum dose of the OAR, $D_{\max, \text{CBCT}}$ is the maximum dose of that OAR on the CBCT, $D_{\max, \text{plan}}$ is the maximum dose of the OAR in the treatment plan and PD is the prescribed dose. For the spinal cord D_{\max} is the maximum dose in any point, for other OARs it is the maximum dose in 1cc. The same formula is used for calculating the relative difference while assuming an invariant dose. In that case $D_{\max, \text{plan}}$ is replaced by $D_{\max, \text{invariant}}$.

7.4 Results

7.4.1 ITV

$V_{100\%}$ was determined by a full dose recalculation using a PTV margin of both 5 mm and 3 mm (figure 7.2a and 7.2b). Using the CBCT before position correction, $V_{100\%}$ was 100% in 65% of the cases when a 5 mm ITV-PTV margin was used and 52% when a 3 mm margin was used. After position correction this amount improved to 98% and 96%, respectively, when margins of 5 mm and 3 mm were used. $V_{100\%}$ was expected to be lower before correction with a 3 mm margin, because with smaller margins, underdosage will occur with smaller set-up errors.

There is no strong correlation between R_{match} and $V_{100\%}$. However, when the margin is used as a cut-off value, there is a significant difference in $V_{100\%}$ between the groups. When a margin of 5 mm was used, the mean value of $V_{100\%}$ was 99.8% (95% confidence interval (CI): 99.6-99.9) when R_{match} was smaller than 5 mm and 89.5% (95% CI: 82.2-96.7) when R_{match} was larger than 5 mm ($p < 0.001$). When a margin of 3 mm was used, the mean values were 99.6% (95% CI: 99.4-99.8) and 91.2% (95% CI: 86.4-96.0) ($p < 0.001$). The means were compared using the Mann-Whitney U test.

7.4.2 OARs

The maximum dose of the OARs was determined in all fractions and compared to the maximum dose in the treatment plan with 5 mm ITV-PTV margins. ΔD_{\max} was in the range of -15% - 10% before position correction (figure 7.3a) and after position correction the majority of the cases is within 5% (figure 7.3b). The effect of the position correction is also within 5% for most cases (figure 7.3c). A paired t-test showed that the effect of the position correction is statistically significant for the spinal cord and the trachea, $p = 0.045$ and $p < 0.001$, respectively.

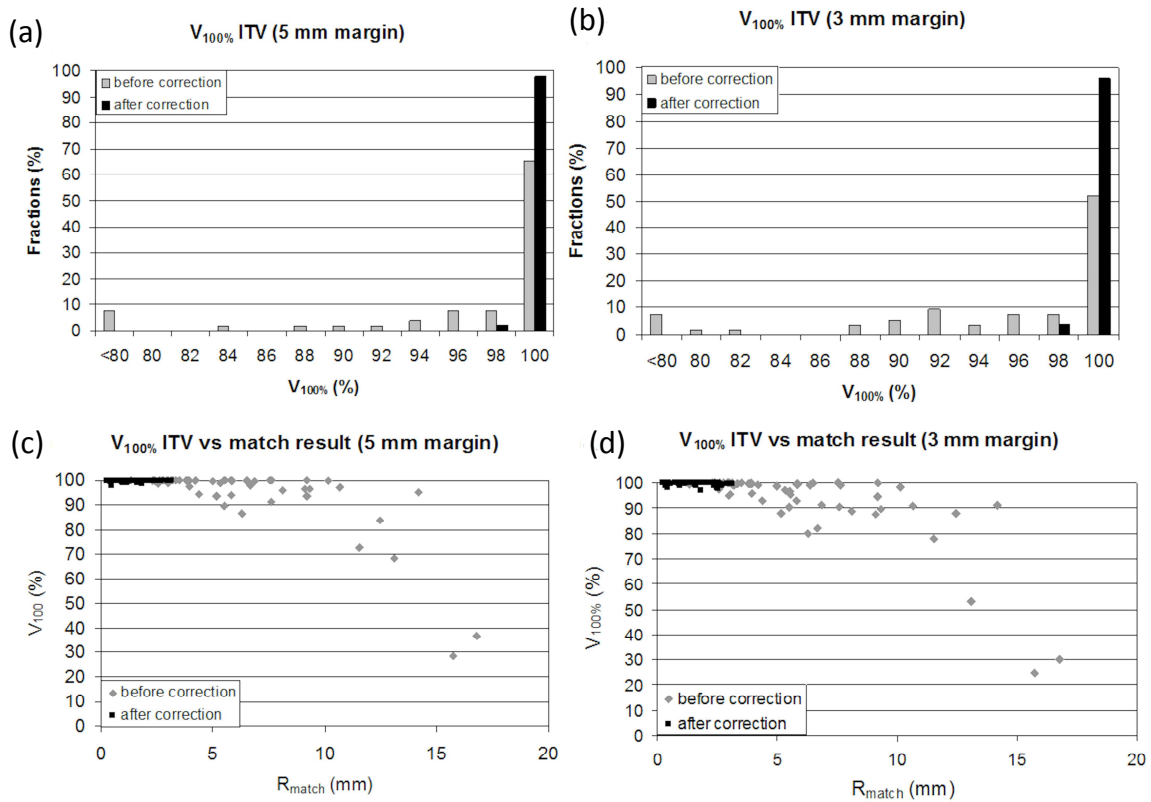


Figure 7.2: The target coverage before and after correction (a) when an ITV-PTV margin of 5mm is applied and (b) when a margin of 3mm is applied. $V_{100\%}$ displayed as a function of R_{match} for (c) a 5mm margin and (d) a 3mm margin.

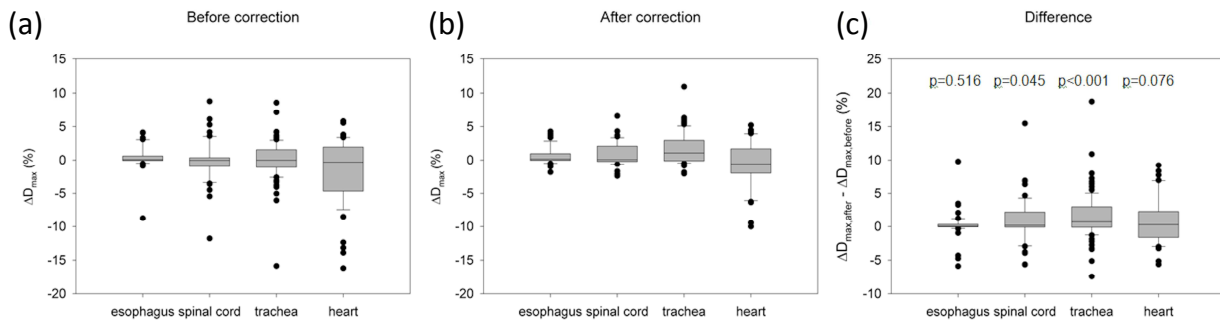


Figure 7.3: ΔD_{max} in the OARs. (a) Before position correction. (b) After position correction. (c) The difference of ΔD_{max} after position correction with ΔD_{max} before position correction. A paired t-test shows a significant difference for the spinal cord and the trachea. The boundary of the box represents the 25th and 75th percentile, the line represents the median and the whiskers represent the 10th and 90th percentile.

7.4.3 Estimation based on invariant dose

For 67% of the cases, there was no difference in $V_{100\%}$ of the ITV between full recalculation and assuming an invariant dose distribution $\Delta V_{100\%}$ (figure 7.4a). No differences occurred mainly for small set-up errors, whereby the assumption of invariant

dose was more likely to be correct. The errors increased with the set-up errors (figure 7.4b) because with large set-up errors, the beams will pass through different body parts than planned. There was no clear relation between $\Delta V_{100\%}$ and R_{match} , because there were also other factors, for example a change in the shape of the patient, that influence $\Delta V_{100\%}$. When the margin was used as cut-off value, the absolute value $|\Delta V_{100\%}|$ was significantly different between the groups. The mean value of $|\Delta V_{100\%}|$ was 0.3% (95% confidence interval (CI): 0.1-0.4) when R_{match} was smaller than 5mm and 3.3% (95%CI: 2.0-4.5) when R_{match} was larger than 5mm ($p < 0.001$). The means were compared using the Mann-Whitney U test. For the OARs the difference between full recalculation of the treatment plan on CBCT and assuming an invariant dose distribution was up to 8% (figure 7.5).

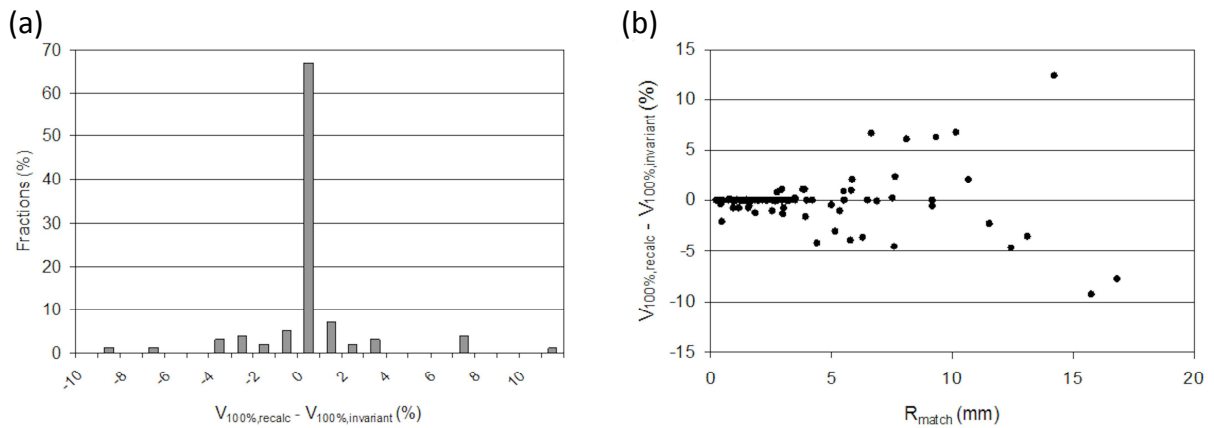


Figure 7.4: (a) A histogram of the relative difference between recalculation of the treatment plan based on CBCT data and the dose based on the assumption of an invariant dose distribution for the ITV. (b) The relative difference between recalculation and assuming an invariant dose distribution for the ITV as a function of the match result.

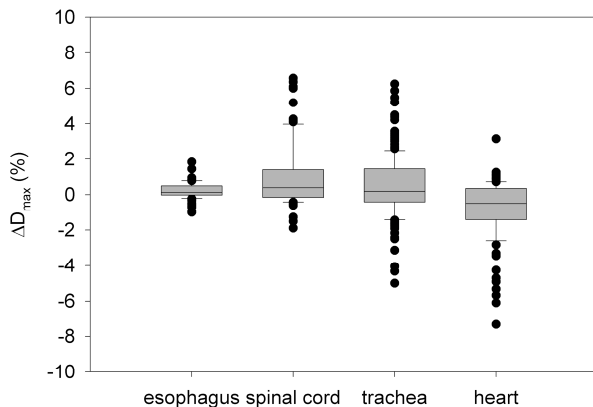


Figure 7.5: The relative difference between full recalculation of the treatment plan on CBCT and assuming an invariant dose distribution for the organs at risk. The boundary of the box represents the 25th and 75th percentile, the line represents the median and the whiskers represent the 10th and 90th percentile.

7.4.4 Errors due to moving OARs

The effect of improper placement of contours of OARs on the CBCT set was estimated by moving the most critical OAR 5mm towards the target. The dose difference in this worst-case scenario was up to 10%. The dose difference was higher when the 'dose before shift' was higher (figure 7.6). This was expected, because the regions with a higher dose were associated with a steeper dose gradient.

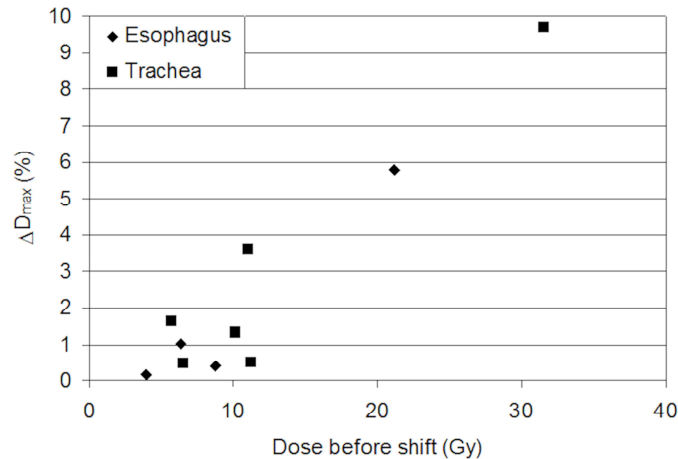


Figure 7.6: The difference in maximum dose in the esophagus and trachea when a shift of 5 mm was applied in the direction of the target. ΔD_{\max} is relative to the prescribed dose.

7.5 Discussion

The goal of this study was to determine the benefits of dose-guided radiotherapy (DGRT) with on-line dose recalculation for stereotactic lung irradiations. DGRT can be used for on-line evaluation of the target coverage and the maximum dose in the OARs. This can be very helpful in the decision making process in cases of substantial changes in the patient's geometry.

Recalculation of the treatment plan on CBCT was compared to an estimation of the dose by superposition of the planned dose on the CBCT dataset. In cases where the set-up error is large, the estimation based on the planning CT can give wrong results. ΔD_{\max} of the OARs is up to 8% when an invariant dose is used instead of a recalculation. This clinically relevant error is probably caused by a movement of the target with respect to the OARs. Another reason for these differences is that with an invariant dose changes in the patient shape are not taken into account.

In the case of SBRT for lung tumors, the contralateral part of the body is often outside the reconstruction volume of the CBCT. Irradiation of the contralateral lung is usually avoided.

In this study none of the beams entered through the missing part of the body. However, this issue might be a limitation for applying DGRT for other treatment sites.

For the purpose of DGRT it is unrealistic to delineate all structures manually. Therefore we copied the structures from the planning CT and shifted them according to the match result. This approximation might cause inaccuracies for the structures that are not fixed to the bony anatomy, in this case the esophagus and the trachea. Therefore we investigated a worst-case scenario on 10 scans to determine the error in the evaluated dose parameter, D_{\max} . The error that was introduced was up to 10%, which is a substantial error. This error increased when the maximum dose increased, resulting in a larger error in the structure that was already close to its critical dose. Note that in reality the error would probably be smaller. We advise that when the dose in an OAR is near the critical dose, to inspect if the match is correct and to adapt the delineation, when necessary. Based on this information a decision on how to proceed can be made.

For the evaluation of the dose in the ITV, two treatment plans were made, one with an ITV-PTV margin of 5 mm and an additional plan with a margin of 3 mm. We chose these margins according to Hurkmans *et al.* who recommend 3-5 mm margin when the ITV concept is used [92]. In our study the ITV is based on a slow CT, combined with a PET-scan. The slow CT takes 4 seconds per cycle and therefore risks missing a part of the tumor when the patient's breathing cycle is slower. The PET-scan on the other hand is truly a slow scan and will reveal possible underestimation of the ITV by the slow CT. Therefore our ITV volumes are expected to be comparable to an ITV volume based on a maximum intensity projection (MIP). Wang *et al.* recommend using a margin of 3 mm when a MIP was used for delineation, so the margin of 5 mm that we use clinically is on the safe side [95]. The acquisition time of a CBCT is 2 minutes, which covers 20-30 breathing cycles, so there is no risk of partial miss of tumor volume on CBCT scans.

Galerani *et al.* also performed a retrospective dosimetric analysis of the actual dose delivered to early stage NSCLC patients who were treated with SBRT [96]. Their numbers are not directly comparable to ours, because they calculated the difference relative to the planned dose in that organ, whereas we calculated the difference relative to the prescribed dose (formula 7.2). However, they also found clinically relevant changes of the dose in the OARs. Therefore they advise to consider both the target and the OAR in the process of image guidance in cases where an OAR is close to the target. No PRV margins were included in this study to compensate for movement of OAR towards the target or vice versa.

Our advice would be to use a PRV margin around each OAR and make sure that the dose within that margin does not exceed the tolerance dose of that OAR. This study shows that when a PRV margin of 10mm is used, ΔD_{\max} in the OARs after position correction is within 5% for the majority of the cases. In accordance with Galerani *et al.*, we advise that the relative movement of the target with respect to the OARs should be considered during the image guidance procedure. In case of doubts an on-line dose recalculation can be used to determine the dose in that specific structure.

DGRT can also be used to determine whether position correction is necessary or not. Our results imply that with a 5 mm ITV-PTV margin 65% of our position corrections would not have been necessary and with a 3 mm ITV-PTV margin this would be 52%. A position correction in our current SBRT protocol takes approximately 5-6 minutes, because after the table correction another CBCT scan is made and analyzed for verification before the actual treatment is started. A prerequisite to actually save time is that DGRT is considerably faster than that. The calculation time in Oncentra for the collapsed cone algorithm when GPU enhancement is used takes approximately 40-50 seconds. The body contour was delineated automatically, but this still took a couple of minutes. The other structures were copied from the planning CT. This makes sense, because no large shape changes for the OARs are expected and tumor regression does not occur until the fourth week of treatment [36], whereas our SBRT schedule for lung tumors takes two weeks at the most. The workflow has to be optimized before the procedure of dose-guided radiotherapy will be an alternative for IGRT.

7.6 Conclusion

DGRT can be a valuable addition to IGRT since it enables evaluation of the dose in the target and the OARs in cases of changes in the patient anatomy. The use of DGRT is recommended in case of large anatomical changes or a set-up error larger than the margin.

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