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CHAPTER 6

SBRT combined with concurrent chemoradiation in stage III NSCLC: feasibility study of the phase I Hybrid trial

ABSTRACT

Purpose
To assess the technical feasibility of the phase I Hybrid trial (NCT01933568), which combines stereotactic body radiotherapy of the primary tumor (PT) and fractionated radiotherapy (FRT) to the lymph nodes (LN).

Materials and Methods
Ten patients with stage II-III NSCLC with a peripheral PT<5 cm diameter were selected. Three treatment plans were compared: conventional fractionated 24x2.75 Gy to PT and LN (IMRT) versus 3x14 Gy (Hybrid low) or 3x18 Gy (Hybrid high) on the PT and 24x2.75 Gy on the LN (VMAT). EQD₂ corrected normal tissue dose parameters were compared using a Wilcoxon signed-rank test. Dosimetric analysis of five Hybrid high treatments was performed.

Results
For all Hybrid low and Hybrid high plans, the average Mean-Lung Dose increased with 1.0 Gy (p=0.050) and 3.1 Gy (p=0.005), and the average spinal cord Dmax decreased with 11.3 Gy (p=0.01) and 10.6 Gy (p=0.03) respectively. For Hybrid low the average esophagus V35 decreased with 4 Gy (p=0.03). All other parameters did not significantly change. Altogether, in eight out of ten patients a Hybrid treatment was feasible. Average pass rates were > 95% for both electronic portal imaging device dosimetry and Octavius.

Conclusions
The combination of SBRT and FRT is feasible and the safety will be assessed in the Hybrid trial.
INTRODUCTION

Stereotactic body radiotherapy (SBRT) results in excellent local control (LC) in early stage non-small cell lung cancer (NSCLC) with 3 year LC rates of >90% and is standard of care in inoperable NSCLC [1, 2]. Unfortunately, one third of patients with NSCLC present with locally advanced (LA) disease and are currently not eligible for SBRT, but receive concurrent chemoradiation (CCRT) if they have a good performance status [3]. Even with modern treatment planning and delivery, two-year local failure rates in these patients remain high at 30% [4, 5]. Several strategies have been pursued to improve LC, but the outcome is only modest compared to SBRT [4, 6, 7].

The combination of SBRT to the primary tumor (PT) and fractionated radiotherapy (FRT) to the lymph nodes (LN) with CCRT has not been explored yet. Therefore we initiated the phase I Hybrid trial (NCT01933568), assessing the safety of combined SBRT to the PT and FRT to the LN with CCRT in LA-NSCLC using a Mean-Lung Dose (MLD) escalation design. The treatment planning of these Hybrid plans is technically challenging, because of the interaction between the dose distribution of SBRT and fractionated therapy, each having a different fractionation schedule. In addition, the resulting complex treatment plan is highly modulated and therefore might possibly lead to dosimetric errors during delivery. Therefore we performed a treatment planning study prior to start of the Hybrid trial, investigating the technical feasibility of a Hybrid treatment, i.e., the delivery of SBRT to the PT and FRT to the LN.

MATERIALS AND METHODS

Patient selection
Ten stage II/III NSCLC patients previously treated in our institution, with nodal involvement and a peripheral PT<5 cm (>2 cm from proximal bronchial tree and mediastinal structures), were randomly selected. Table 1 shows details of the PT and LN localizations.

Treatment preparation
Patients were positioned in supine position using an arm- and knee-support. A 4D-planning CT scan with contrast and 3mm slice-thickness was acquired with the patient in treatment position. The PT peak-to-peak amplitudes in three directions were derived from local rigid registration of the 4D CT scan. A mid-ventilation CT scan was reconstructed from the 4D CT scan, with the tumor closest to its time-weighted mean position, and used for tumor delineation and treatment planning [8]. For delineation the diagnostic FDG PET/CT was registered with the mid-ventilation CT. Mediastinal and lung window-level were available and PT and LN delineations were performed and checked by a second dedicated radiation oncologist. The anisotropic GTV-PTV expansion was based on the margin recipe of van
Herk et al. [9]. For the conventional plans, PTV_{PT,conv} was created by expanding the GTV using margins of 12 mm plus ¼ of the GTV-PT peak-to-peak amplitude in orthogonal directions, as observed in the 4D CT scan. For the LN an isotropic PTV_{LN,conv} was created using a margin of 12 mm. PTV_{PT,conv} and PTV_{LN,conv} were combined to a total PTV_{tot,conv}. For the Hybrid plan, the GTV-PTV_{PT,hyb} margin was 8-8-9 mm in left-right (LR), cranio-caudal (CC) and anterior-posterior (AP) direction respectively, for an amplitude of 0 mm with a non-linear increase for larger respiratory tumor motion amplitudes [10, 11]. The PTV_{LN,hyb} margin was 8-9-9 mm, similar as described by Schaake et al. [12].

**Table 1.** Tumor and treatment characteristics

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Tumor location</th>
<th>TNM* Stage</th>
<th>Involved nodal stations</th>
<th>PTV_{tot,conv} (cc)</th>
<th>PTV_{PT,hyb} (cc)</th>
<th>PTV_{LN,hyb} (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LUL T1aN3 IIIB</td>
<td>1, 2R, 4L, 4R, 6, 10L</td>
<td>432.5</td>
<td>29.0</td>
<td>300.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RUL T1aN3 IIIA</td>
<td>4L</td>
<td>219.7</td>
<td>32.7</td>
<td>134.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RLL T1bN2 IIIA</td>
<td>2R, 4R, 10R</td>
<td>311.0</td>
<td>91.9</td>
<td>139.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RLL T2aN1 IIIA</td>
<td>10R</td>
<td>157.3</td>
<td>69.6</td>
<td>44.1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>RUL T1aN2 IIIA</td>
<td>4R, 10R</td>
<td>293.1</td>
<td>17.5</td>
<td>224.8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RUL T1bN2 IIIA</td>
<td>2R, 3R, 4R, 7, 10R</td>
<td>471.1</td>
<td>69.5</td>
<td>290.0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>RLL T2aN3 IIIB</td>
<td>4R, 4L, 7, 10R</td>
<td>354.9</td>
<td>82.7</td>
<td>188.5</td>
<td></td>
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<tr>
<td>8</td>
<td>RUL T2aN3 IIIB</td>
<td>1, 2R, 3R, 4R, 7, 10R</td>
<td>527.0</td>
<td>62.1</td>
<td>355.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>RUL T1aN3 IIIB</td>
<td>1, 2R, 2L, 4L, 6, 10R</td>
<td>818.3</td>
<td>22.0</td>
<td>627.3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>RUL T1aN3 IIIB</td>
<td>1, 2R, 2L, 3, 4R</td>
<td>603.2</td>
<td>28.0</td>
<td>466.8</td>
<td></td>
</tr>
</tbody>
</table>

* 7th TNM edition

PTV_{tot,conv} = total PTV of the conventional treatment plan, PTV_{PT,hyb} = primary tumor PTV of the Hybrid treatment plan, PTV_{LN,hyb} = lymph node PTV of the Hybrid treatment plan. RUL=right upper lobe, RLL=right lower lobe, LUL=left upper lobe.

**Conventional radiotherapy treatment planning**

Our standard treatment for LA-NSCLC consists of 24x2.75Gy with daily intravenous cisplatin 6 mg/m² with an overall treatment time (OTT) of 32 days. All patients receive image guided Intensity Modulated Radiotherapy (IMRT). Treatment plans were optimized by experienced dosimetrists with Pinnacle version 9.2 (collapsed cone convolution superposition algorithm) using seven 10 MV beams with a maximum of four segments per beam. Dose was prescribed to the ICRU reference point, located on a representative position in PTV_{tot,conv}. Target coverage was considered acceptable if 99% of the PTV received at least 90% of the prescribed dose, with target coverage of the 95% isodose line to the target in mediastinal tissue and 90% to the target where it is surrounded by the lung tissue [13]. A dose inhomogeneity of up to 115% in the PTV was accepted [14].
Hybrid treatment planning

Our standard treatment for stage I peripheral NSCLC is 3x18 Gy, with at least a 48-hour interval between fractions and an overall treatment time (OTT) of eight days. To enable simultaneous optimization of the different fractionation regimens used in the Hybrid treatment, a VMAT technique was used for both the PT as the LN.

For each patient, two Hybrid plans were created that differed in the dose to the PT: either 3x14 Gy or 3x18 Gy. The low dose level of 42 Gy is a conservative estimation of the biologically equivalent dose of 24x2.75 Gy using the LQL-model (α/β=10 Gy and d$_{t}$=7 Gy). Each Hybrid plan consisted of three different components: 1) an FRT plan delivering 21 fractions of 2.75 Gy to the LN with the isocenter at the center of mass of PTV$_{LN,hyb}$; 2) an FRT plan delivering 3 fractions of 2.75 Gy to the LN (same isocenter as plan 1); 3) an SBRT plan delivering 3 fractions of either 14 Gy or 18 Gy to the PT with the isocenter in the PTV$_{PT,hyb}$. We started the planning with component 1) and 2), prescribing 21x2.75 Gy and 3x2.75 Gy to the LN, respectively. Dose was described to a representative point in PTV$_{LN,hyb}$ and it was required that V90≥99%. Second, component 3), the SBRT plan to the PT was made. Dose was prescribed to the isodose line encompassing 95% of PTV$_{PT,hyb}$, accepting a maximum dose up to 165% (within the GTV). The prescription dose of the PT was corrected for the unintended dose to the PT due to the LN plan (21 fractions) as obtained in the first step of treatment planning. To that end, the minimal (D$_{99}$) EQD$_{2}$ ($\alpha/\beta=10$ Gy) LN dose to PTV$_{PT,hyb}$ was subtracted from the prescribed EQD$_{2}$ to PTV$_{PT,hyb}$. Subsequently, the SBRT plan was combined with the LN plan delivering 3 fractions, yielding a total plan for 3 fractions. The dose distribution of the latter plan was finely tuned by performing a ‘warm’ start optimization on the existing beam segments. Finally, the plan for 3 fractions was combined with the LN plan for 21 fractions, yielding the total dose distribution for the whole series. This resulting total dose distribution was evaluated with respect to target coverage and dose to organs at risk (OAR).

Constraints

The MLD was calculated over both lungs minus GTV after voxel-wise EQD$_{2}$ correction ($\alpha/\beta=3$ Gy). The mediastinal OAR including vessels, esophagus, heart, trachea and proximal bronchial tree was delineated as one volume: the mediastinal envelope (ME). To account for geometrical uncertainties, a Planning organ-at-risk volume (PRV$_{ME}$) was created with a margin of 5 mm. For the PRV$_{ME}$, a D$_{max}$ of 115% of 66 Gy was accepted, corresponding to an EQD$_{2}$=94 Gy ($\alpha/\beta=3$ Gy). Other important constraints were spinal cord (SC) D$_{max}$=50 Gy ($\alpha/\beta=2$ Gy) and an MLD$_{≤20}$ Gy ($\alpha/\beta=3$ Gy). Other parameters used for dose evaluation were the esophagus V35 ($\alpha/\beta=10$ Gy), the V20 and the V5 of the lung (physical dose) as well as the mean heart dose ($\alpha/\beta=3$ Gy).
Dosimetry
To validate the correspondence between the planned and delivered dose distribution for the Hybrid high plans, dosimetry was performed in five randomly selected patients (patient #4, 6, 7, 9 and 10) using two different methods. In the first method, the plans were delivered to the Octavius-II phantom with an Octavius 729 detector array (PTW, Freiburg, Germany). This phantom uses a 2D array of 729 ionization chambers with 10 mm spacing and therefore has the ability to measure absolute dose with high accuracy. In the second method, the dose distribution was measured in a rectangular phantom made of polystyrene using our in-house developed electronic portal imaging device (EPID) transit dosimetry method [15]. For both Octavius and EPID, measured and planned dose distributions were compared using a gamma analysis with a 3%/3mm criterion. For Octavius, 2D dose distributions within the 5% isodose line of the measured maximum dose were compared in a coronal plane through the isocenter. For EPID, 3D dose distributions were compared within the 50% isodose volume of the planned maximum dose. The three Hybrid plan components were measured and analysed separately and analysis was performed per arc.

Statistics
Treatment planning results were compared between the conventional plan, the Hybrid low and the Hybrid high treatment plan with a Wilcoxon signed-rank test using SPSS software (IBM SPSS version 24). Results with a p-value <0.05 were considered to be statistically significant.

RESULTS

Conventional radiotherapy treatment plans
In all ten patients target coverage of PTV_{tot, conv} was excellent and the V90≥99% constraint was met. Constraints on OARS were met in all patients, except for a small violation of SC D_{max} (50.2 Gy) in one patient (#8), which was considered acceptable.

Hybrid treatment plans
In all Hybrid plans target coverage was excellent for both the PTV_{PTV, hyb} (V100%≥95%) and the PTV_{LN, hyb} (V90%≥99%). Figure 1 shows an example of a Hybrid plan and for comparison the conventional plan. Notice that in the Hybrid plan, the 90% and 95% isodose lines around the PTV_{LN, hyb} become slightly less conformal at the level of PTV_{PTV, hyb}. With respect to OAR constraints, the Hybrid low treatment plan was feasible in eight patients. In one patient (#7) the D_{max} of the PRV_{ME} was violated (112 Gy), in another (#8) the MLD exceeded the constraint (23.3 Gy).

The Hybrid high treatment plan was feasible in five patients. As expected patient #7 and #8 had an even higher PRV_{ME} dose and MLD than in the Hybrid low treatment plan (115 Gy
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and 24.1 Gy respectively). Patient #3 exceeded the MLD constraint (20.6 Gy). Patient #6 had a combination of a too high PRVME dose and MLD of 102 Gy and 23.6 Gy respectively and patient #9 violated the SC and PRVME constraints with values of 50.9 Gy and 94.7 Gy respectively.

**Comparison of treatment plans**

The DVH parameters of the conventional plans versus Hybrid low and Hybrid high of all ten patients are displayed and compared in table 2. The Hybrid treatment plans resulted in a significant increase of the MLD with 3.1 Gy (p=0.005) for Hybrid high and 1.0 Gy for Hybrid low (p=0.050). In figure 2 the effect of the addition of SBRT and the modulation of the SBRT fraction size on the MLD is displayed per patient. There was a significant decrease in the spinal cord dose in both Hybrid plans and of the esophagus V35 in the Hybrid low plans. All other constraints, including the PRVME D_{max}, were not significantly different.

![Figure 1](image_url)

**Figure 1.** Hybrid treatment plan in axial (a) and coronal view (b): primary tumor (PTV_{hyb, purple}) 3x18 Gy and lymph node (PTV_{hyb, pink}) 24x2.75 Gy. For comparison the conventional plan with 24x2.75 Gy to PTV_{conv, pink}, axial (c) and coronal (d). In the legend the absolute values of the total biological dose (α/β=10 Gy) and their corresponding percentages are given, e.g. 150% (red) isodose line=189 Gy, 100%(orange)=126 Gy etc.
Table 2: Comparison of DVH parameters (mean±standard deviation) between the conventional treatment plan (conv), the Hybrid low (SBRT dose 3x14 Gy) and Hybrid high (SBRT dose 3x18 Gy) of all 10 patients.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Parameter</th>
<th>Constraint</th>
<th>$\alpha/\beta$ (Gy)</th>
<th>conv</th>
<th>Hybrid low</th>
<th>Hybrid high</th>
<th>$\Delta_{\text{Hybrid low &amp; conv}}$</th>
<th>p-value</th>
<th>$\Delta_{\text{Hybrid high &amp; conv}}$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>MLD</td>
<td>≤20 Gy</td>
<td>3</td>
<td>14.9 ± 3.7</td>
<td>15.9 ± 4.7</td>
<td>18.0 ± 4.9</td>
<td>1.0 ± 1.9</td>
<td>0.05</td>
<td>3.1 ± 2.0</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>∞</td>
<td></td>
<td>29.0 ± 7.1</td>
<td>26.5 ± 9.5</td>
<td>27.3 ± 9.2</td>
<td>-2.5 ± 3.8</td>
<td>0.09</td>
<td>-1.7 ± 3.7</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>V5</td>
<td>∞</td>
<td></td>
<td>57.6 ± 9.7</td>
<td>57.5 ± 10.4</td>
<td>58.7 ± 10.4</td>
<td>-0.08 ± 4.5</td>
<td>0.72</td>
<td>1.2 ± 4.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Dmax</td>
<td>≤50 Gy</td>
<td>2</td>
<td>46.8 ± 2.8</td>
<td>35.5 ± 10.6</td>
<td>36.1 ± 10.6</td>
<td>-11.3 ± 3.5</td>
<td>0.01</td>
<td>-10.6 ± 3.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Esophagus</td>
<td>V35</td>
<td>≤65 %</td>
<td>10</td>
<td>41.6 ± 17.6</td>
<td>37.6 ± 15.7</td>
<td>39.1 ± 15.7</td>
<td>-4.0 ± 7.5</td>
<td>0.03</td>
<td>-2.5 ± 7.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Heart</td>
<td>Dmean</td>
<td>≤46 Gy</td>
<td>3</td>
<td>5.8 ± 2.7</td>
<td>5.2 ± 2.7</td>
<td>5.4 ± 2.5</td>
<td>-0.5 ± 1.2</td>
<td>0.31</td>
<td>-0.4 ± 1.2</td>
<td>0.31</td>
</tr>
<tr>
<td>PRV$_{\text{ME}}^*$</td>
<td>Dmax</td>
<td>≤94 Gy</td>
<td>3</td>
<td>83.3 ± 4.5</td>
<td>87.9 ± 9.7</td>
<td>93.0 ± 14.0</td>
<td>4.6 ± 3.4</td>
<td>0.17</td>
<td>9.7 ± 4.7</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Mediastinal envelope (ME)=large vessels, esophagus, heart, trachea and proximal bronchial tree. Planning organ-at-Risk Volume (PRV)=ME+5mm
D= delta (difference)
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Figure 3 illustrates that if the PTV_{PT,hyb} and PTV_{LN,hyb} distance becomes smaller, the D_{max} of PRV_{ME} becomes higher. It was estimated that at least a distance of 3 cm between PTV_{PT,hyb} and PTV_{LN,hyb} was necessary, in order not to exceed the PRV_{ME} constraint.

Figure 3. Relation between the D_{max} in the Planning organ-at-Risk Volume of the mediastinal envelope (PRV_{ME}) (α/β=3 Gy) and distance between the primary tumor PTV (PTV_{PT,hyb}) and the closest lymph node in any plane (PTV_{LN,hyb}) for the Hybrid high treatment plan. Dotted line indicates the PRV_{ME} constraint of 94 Gy.

Dosimetry
Table 3 summarizes the results of the dosimetry for Octavius and EPID outcomes. For Octavius, the average value and range of the pass rate (95γ ≤ 1.0, percentage of datapoints having a γ-value ≤ 1.0) over 5 patients is given. For EPID dosimetry, the average values and ranges over 5 patients are given for the mean value of γ (γ_{mean}), the pass rate, the 1% highest maximum γ (γ_{1%}), and the percentage dose difference in the isocenter (ΔD_{isoc} measured-planned).
Average pass rates were > 95% for all three plan components for both EPID dosimetry and Octavius. For EPID dosimetry, the average $\gamma_{\text{mean}}$ for all three plan components was well below 0.5, indicating dosimetric agreement within 1.5%/1.5mm. $\gamma_{1\%}$ ranges from 0.81 to 1.57, the highest value caused by occasional hot spots in the measured dose distribution. Finally, a systematic small underdosage was measured in the isocenter for the 21x2.75 Gy and 3x18 Gy plan components.

**DISCUSSION**

We successfully conducted a treatment planning study of a Hybrid treatment, combining SBRT to the PT and FRT to the LN. A Hybrid treatment plan was feasible in eight out of ten patients at the cost of a higher MLD. In the phase I Hybrid trial (NCT01933568), the MLD will be escalated depending on the observed lung toxicity, with a starting MLD≤18 Gy. Due to the novelty of the Hybrid treatment in clinical practice, we chose to be more conservative with regard to the MLD≤20 Gy used in this analysis, which is compliant with our clinical practice for LA-NSCLC. As shown, reduction of the SBRT fraction size is a useful tool to decrease the MLD. If applying the MLD≤18 Gy constraint to our treatment planning study cohort, six patients would have been eligible for the trial. Within the trial SBRT fraction size will be modulated between 14-18 Gy until the maximally allowed MLD is reached, enabling individual dose escalation.

The PRV$_{\text{ME}}$ constraint was violated in several patients, but not significantly increased, probably due to our patient selection with peripheral tumors only. We estimated that a minimum distance of 3 cm between PTV$_{PT,\text{hyb}}$ and PTV$_{LN,\text{hyb}}$ is necessary for a patient to be eligible for the Hybrid trial (figure 3). Although the distance between the PTV$_{PT,\text{hyb}}$ and the PRV$_{\text{ME}}$ is more

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**Table 3.** Results of EPID dosimetry and Octavius of Hybrid plan components. Average value and range is given for $\gamma$ parameters and isocenter dose difference over 5 patients.

<table>
<thead>
<tr>
<th></th>
<th>21 x 2.75 Gy to LN</th>
<th>3 x 2.75 Gy to LN</th>
<th>3 x 18 Gy to PT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPID dosimetry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_{\text{mean}}$</td>
<td>0.42 (0.32 - 0.51)</td>
<td>0.43 (0.32 - 0.52)</td>
<td>0.44 (0.32 - 0.52)</td>
</tr>
<tr>
<td>$%\gamma \leq 1.0$</td>
<td>97 (91.7 - 99.7)</td>
<td>97 (94.6 - 99.8)</td>
<td>96 (92.7 - 99.9)</td>
</tr>
<tr>
<td>$\gamma_{1%}$</td>
<td>1.17 (0.88 - 1.48)</td>
<td>1.12 (0.89 - 1.39)</td>
<td>1.27 (0.81 - 1.57)</td>
</tr>
<tr>
<td>$\Delta D_{\text{ req}}$(%)</td>
<td>-1.1 (-3.1 - +0.8)</td>
<td>0.62 (-2.5 - +3.6)</td>
<td>-1.44 (-3.8 - +0.2)</td>
</tr>
<tr>
<td><strong>Octavius</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$%\gamma \leq 1.0$</td>
<td>99.6 (97.8 - 100)</td>
<td>99.8 (98.6 - 100)</td>
<td>99.7 (99.0 - 100)</td>
</tr>
</tbody>
</table>

LN= lymph nodes  
PT= primary tumor
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relevant, we chose a practical ‘rule of thumb’ prior to start of the extensive treatment planning procedure and OAR delineation.

The dosimetry results of the Hybrid high plan components show that the treatment planning system can cope very well with the high modulation required to produce acceptable plans. On average, the γ statistics are well within the constraints used in our clinic, which were γmean ≤ 0.5, pass rate ≥ 95%, γ1% ≤ 2. Violations of these constraints can be seen in table 3, but in all cases these violations were minor and only present in one arc of a plan component, while the other arc was within the constraints. A systematic small underdosage is measured in the isocenter for the 21x2.75 Gy and 3x18 Gy plan components. However, in most cases the isocenter lies in a region with high dose gradient, making a point dose measurement sensitive to small position errors. This effect also explains the relative large range in ΔDisoc.

Different margins were used for PTV_{PT,hyb} and PTV_{PT,conv}, which explains the significant spinal cord dose decrease in both Hybrid plans and possibly the esophagus V35 decrease in the Hybrid low plan. The rational for different margins was that in the conventional plan one isocenter was used for both the PT as the LN with an online carina match imaging protocol. Due to differential motion of the PT with respect to the carina, a relative larger margin around the PT is necessary. In the Hybrid treatment two isocenters were used and an on-line soft tissue match will be performed of both the PT as the carina, thus increasing delivery accuracy and allowing for a margin decrease. To account for difference between the setup for the two different isocenters, a 5 mm PRV margin was used for the ME.

There are different strategies to plan and deliver a Hybrid treatment. We chose to do a simultaneous optimization of the three LN fractions and the SBRT plan, which has the advantage of taking into account the unintended dose of the LN plan to the PT. Although this strategy might be more complicated and time consuming than e.g. planning and delivering an SBRT plan and a fractionated LN plan sequentially, we thought this was the most thorough and safest strategy. Moreover, creation of a total dose distribution for the whole treatment series is essential. Because of the different fractionation schedules of the FRT and hybrid components of the Hybrid plans, conversion to EQD₂ is essential to correctly calculate dose to OAR. All results reported are based on the assumption we used the correct α/β ratio’s and that the LQ-model for OAR and the LQL-model for tumor are applicable in SBRT [16-18].

To our knowledge we are the first to report about a successful simultaneous treatment planning procedure of SBRT and FRT. Two studies reported feasibility and tolerability of a sequential SBRT boost after CCRT in LA-NSCLC with a 3-4 week treatment gap [19, 20]. We believe that the combination of FRT and SBRT could be an efficient strategy for dose escalation by decreasing the overall treatment time compared to fractionated dose escalation studies [21]. Moreover, high dose to the mediastinal tissue can be avoided (e.g. heart, esophagus),
which often causes severe toxicity in both FRT as SBRT [4, 22-24]. Finally, smaller margins used in SBRT may even decrease toxicity as observed in the SPACE trial comparing SBRT and FRT for early stage NSCLC [25] or it could limit a possible toxicity increase when combining SBRT with chemotherapy. However, whether this is true will be tested in the phase I Hybrid trial.

In conclusion, results of our treatment planning study show that the combination of SBRT to the PT and FRT to the LN in LA-NSCLC is feasible at the cost of an increased MLD. The safety of this approach will be tested in the phase I Hybrid trial. Results of this trial may result in a broader application of SBRT in LA-NSCLC, such that more patients benefit from the excellent LC achieved with SBRT compared to conventional FRT.

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