Improving the Therapeutic Ratio of Stereotactic Body Radiotherapy for Centrally Located Non-Small Cell Lung Cancer

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JULY 12–16 2020 VIRTUAL
JOINT AAPM | COMP MEETING
EASTERN TIME [GMT-4]

INTRODUCTION

Stereotactic body radiation therapy (SBRT) for central and ultra-central non-small cell lung cancers (NSCLC) can be associated with high risks of extreme and potentially fatal toxicities because of proximity to critical organs (1). Trade-off approaches prioritizing organs at risk (OARs) sparing over target coverage can maintain high rates of local control with acceptable toxicity (2). However, toxicity remains a real concern, and the trade-off indications may be unclear (4). In the current work, we investigated the feasibility and dosimetric effects of systematically reducing the planning target volume (PTV) margins as an essential step to improving the therapeutic window for the SBRT of centrally located NSCLC. This approach may help designing more systematic standardization of dosimetric and radiobiological optimization strategies.

AIM

For lung SBRT, PTV is determined by expanding the internal gross tumor volume (IGTV) by a typical margin of 5 mm. This work aimed to i) investigate the dosimetric effects of reducing the PTV margin to 2 mm on normal tissue sparing and on tumor coverage, ii) assess the impact on the tumor dose coverage by tracking the fraction doses using the cone-beam CT (CBCT) images.

METHOD

Ten patients with early-stage NSCLC were selected. The internal gross tumor volume (IGTV) was defined using 4DCT images. To reduce delivery uncertainties, we only considered ungated cases with tumor motion less than 7 mm. The planning target volume margins were 5 mm for the clinical plans (PTV_{5mm}) and 2 mm for the reduced margin test plans (PTV_{2mm}). The dose prescription was 60 Gy in 8 fractions. Dose objectives for the test plans where: i- At least 99% of the PTV_{2mm} covered by the prescription dose, ii- 100% of the IGTV covered by the prescription dose. For the clinical plans, at least 95% of the PTV_{5mm} was covered by the prescription dose.

We used CBCT verification images to assess the IGTV dose coverage for each treatment fraction.

Dose-volume histogram (DVH) parameters most correlated with toxicity were recorded for the esophagus, proximal bronchial tree (PBT), great vessels, heart, spinal cord, lung, and chest wall. Equivalent 2 Gy doses (EQD_2) and biologic effective doses (BED) were calculated based on the linear-quadratic model.

RESULTS

Dose evaluation:

- Intermediate and low dose volumes were significantly reduced in $Plan_{2mm}$ cases. Fig. 1 shows an example of dose distributions and DVHs for $Plan_{2mm}$ (test plans) and $Plan_{5mm}$ (clinical plans)
- $D_{99\%}$ for the IGTV was similar for both $Plan_{2mm}$ and $Plan_{5mm}$ (Fig. 2).
- The mean dose to the proximal normal tissue was, on average, 8 Gy lower for $Plan_{2mm}$. The median BED was reduced by 35% (from 67.7 Gy_3 to 43.7 Gy_3) (Fig. 2).
- For the proximal bronchial tree (PBT), the D_{3cc} median value was reduced from 23.3 Gy to 10.7 Gy. The highest dose sparing was 19.7 Gy. The dose reduction in EQD_2 was from 24.5 Gy to 8.1 Gy (16.4 Gy) (see Fig. 3).
- For the great vessels, The D_{1cc} was reduced from 48.7 Gy to 34.6 Gy. The highest difference was 24 Gy. The dose reduction in EQD_2 was from 55.8 Gy to 33.1 Gy (22.7Gy).
- For the Esophagus, The D_{1cc} was reduced from 14.8 Gy to 8.6 Gy. The highest difference was 16.5 Gy. The dose reduction in EQD_2 was from 14.6 Gy to 7.9 Gy (6.7Gy).
- The dose to the cord and the heart were generally well below their respective dose constraints. However, $Plan_{2mm}$ still showed significant sparing of these organs with a reduction, for instance, of the D_{max} up to 9 Gy for the spinal cord (median 4.7 Gy) and up to 22.4 Gy for the heart (median 5.3 Gy).
- The maximum dose to the chest wall was reduced by up to 17.4 Gy. The D_{1cc} median value was decreased by 8.3 Gy (range, 5.4– 13.6).

Dose tracking:

- The IGTV volume covered by 100% of the prescription dose ($V_{100\%}$) was at least 99.6% for al treatment fractions.
- All $D_{99\%}$ values for the IGTV were above the 100% prescription dose. The dose variation among CBCT images was less than 0.5 Gy (median 0.2 Gy) (see Fig. 4).

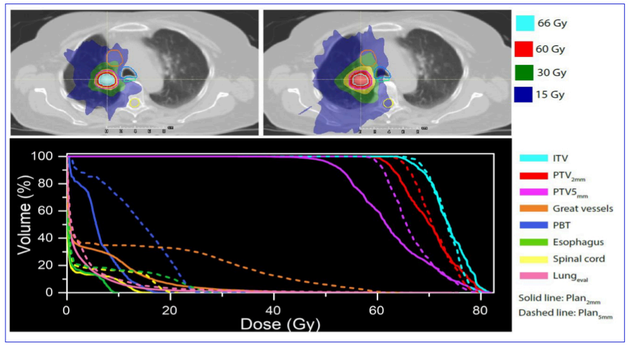

***Figure 1**: (Top raw) Example of dose distributions for patient 10 for $plan_{2mm}$ (left) and $Plan_{5mm}$ (right). (Bottom row) Dose-volume histogram showing the dose to target volumes and critical OARs for both $plan_{2mm}$ and $Plan_{5mm}$.*

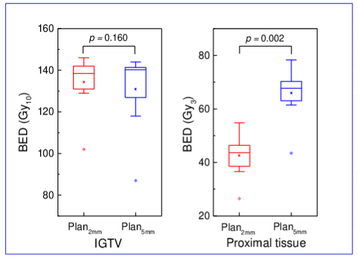

***Figure 2**: Box and whisker graph showing the biologic effective dose (BED) calculated based on the mean dose to the IGTV ($\alpha/\beta = 10$) and to the proximal tissue (2 cm thick shell around the PTV_{5mm}) ($\alpha/\beta = 3$).*

The box is determined by the 25th and the 75th percentiles. The whiskers are determined by the 5th and 95th percentiles. The line within the box and the closed square represent the median and the mean values, respectively. P is the P value of the signed Wilcoxon signed rank test.

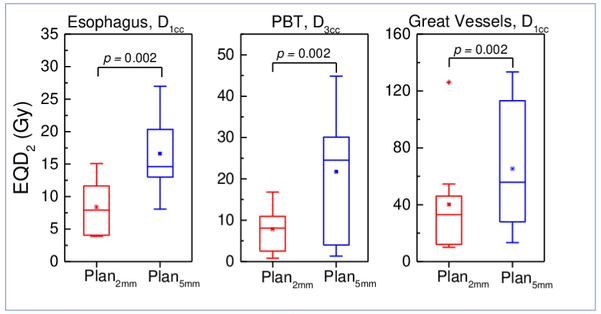

***Figure 3**: Box and whisker graph showing the EQD_2 dose to a volume of x cm^3 (D_{xcc}) for the esophagus ($\alpha/\beta = 10$), great vessels ($\alpha/\beta = 3$) and the proximal bronchial tree (PBT) ($\alpha/\beta = 3$).*

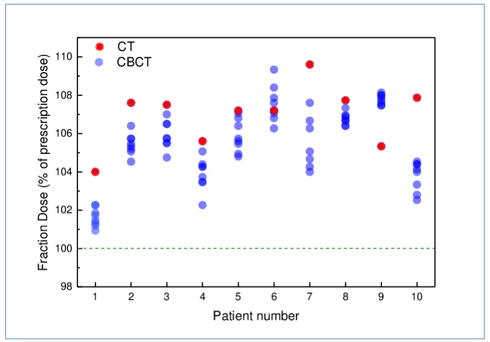

***Figure 4:** Dose to 99% of the IGTV ($D_{99\%}$) as percentage of the prescription fraction dose. Red circles represent the planned fraction dose on the planning CT images. Blue circles represent the delivered dose for each treatment fraction calculated on the CBCT.*

CONCLUSIONS

- Reducing the PTV margin to 2 mm allowed for a significant reduction of the dose burden to the normal tissue surrounding the tumor and of the dose to critical organs without compromising tumor coverage.
- The dose sparing might help to minimize toxicity to critical organs such as the PBT, great vessels, and esophagus.
- High and consistent tumor coverage can be ensured by specifying minimum dose objectives for the IGTV and by designing high dose gradients in the planning process.
- Reducing the PTV margin with a suitable planning strategy can significantly improve the therapeutic window, potentially allowing for safer dose escalation to the tumor and improvement of treatment efficiency.
- Based on CBCT inter-fraction tracking of patient anatomy and position, tumor coverage can be maintained within the 2 mm margin throughout the treatment course. We did not assess intra-fraction variations in the current study.
- Shorter treatment deliveries and advancements in intra-fraction monitoring are significantly improving the accuracy of treatment delivery within a 2 mm margin (5).

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