PHYSICS CONTRIBUTION

FEASIBILITY OF HELICAL TOMOTHERAPY IN STEREOTACTIC BODY RADIATION THERAPY FOR CENTRALLY LOCATED EARLY STAGE NON–SMALL-CELL LUNG CANCER OR LUNG METASTASES

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Purpose: To investigate the ability of helical tomotherapy (HT) to spare critical organs immediately adjacent to the tumor target in stereotactic body radiation therapy (SBRT) for centrally located lung lesions.

Methods and Materials: HT SBRT plans for 10 patients with centrally located lesions or lesions immediately adjacent to a critical structure were generated. A total of 70 Gy in 10 fractions was prescribed to the planning target volume (PTV) to satisfy a target volume coverage of ≥95% PTV receiving 70 Gy and an established set of dose constraints for the organs at risk (OARs). Quality assurance (QA) of the HT plans was performed with both ion chamber and film measurements.

Results: The PTV coverage criteria was met with 95% of the PTV receiving 70.68 ± 0.33 Gy for all cases even though the OARs immediately adjacent to the PTV ranged from 0.38 to 0.85 cm away. The mean lung dose (MLD), and V20 were 7.15 ± 1.44 Gy, and 11.93 ± 3.24 % for the total lung, respectively. The dose parameters of MLD, V5, V10, and V20 for the contralateral lung were significantly lower than those for the ipsilateral lung (p < 0.05). An average dose fall off from the PTV periphery to the edge of the immediately adjacent OAR was 47.6% over an average distance of 4.87 mm. Comparison of calculated and measured doses with the ion chamber showed an average of 1.85% point dose error, whereas an average mean gamma and the area with a gamma larger than 1 of 0.20 and 0.94% were observed, respectively.

Conclusion: HT allows the sparing of critical structures immediately adjacent to the tumor target, thus making SBRT for these centrally located lesions feasible. © 2011 Elsevier Inc.

INTRODUCTION

Early-stage non–small-cell lung cancer (NSCLC) has been treated by stereotactic body radiation therapy with excellent clinical outcome (1). Generally, local control of over 80% has been demonstrated when a biologically effective dose (BED) of ≥100 Gy10 (BED calculated with α/β of 10) was delivered to the tumor target (2–5). Despite the excellent local control, Grade 5 toxicity has been observed when centrally located lesions have been treated with 60–66 Gy delivered over three fractions (6, 7); prompting some institutions to recommend that SBRT should be contraindicated for such lesions. However, this exclusion criterion would deprive many patients with early-stage NSCLC of an optimal outcome. Thus, a treatment modality that effectively spares the central critical structures from excessive radiation toxicity while delivering a high BED to the tumor would be ideal.

Intensity-modulated radiation therapy (IMRT) allows for the delivery of pencil beams with various intensities to achieve a highly conformal dose distribution within the tumor target volume. As a result, it can create a sharp dose gradient adjacent to the high-dose region, which in many cases, effectively spares the adjacent normal structures. IMRT has been associated with excellent clinical outcome and normal tissue sparing (8, 9). Therefore, intensity modulation may provide a great advantage in avoiding severe complications in the delivery of SBRT for centrally located lung lesions. In fact, intensity-modulated SBRT was already shown to have excellent local control and minimal severe late toxicity (1 Grade 3 dyspnea) after 3 years in a study of mostly peripheral lesions (10).

Helical tomotherapy (HT) is a technology that delivers fan-beam IMRT under megavoltage computed tomography...
(MVCT) guidance through continuous and synchronous gantry rotation and couch movement during radiation delivery (11). With HT, IMRT is delivered in a helical manner similar to that of a spiral CT, whereas integrated online MVCT permits daily correction of interfractional variation, assessment of internal movement, and reconstruction of the delivered dose (12). More importantly, HT optimizes intensity modulation through 51 angles per gantry rotation, thereby generating highly conformal dose-avoidance of critical organs while achieving excellent target volume coverage in regions of complex geometry. Dosimetrically, HT has been shown to improve dose homogeneity and decrease doses to the organs at risk (OARs) when compared to conventional linac-based IMRT (13–15). Clinically, SBRT delivered through HT has demonstrated excellent toxicity profile in the treatment of peripheral early-stage NSCLC and lung metastases (16, 17). Thus, HT may potentially improve OAR sparing to allow the safe delivery of SBRT for centrally located lesions. This might be proven invaluable especially when the tumor target volume is immediately adjacent to the critical structures.

In this dosimetric study, we explore HT’s ability to spare the OARs in the treatment planning of SBRT for centrally located lung lesions, which are immediately adjacent to critical normal structures.

**METHODS AND MATERIALS**

**Patient and tumor characteristics**

Ten patients with centrally located lesions or lesions adjacent to critical structures were selected. These patients had undergone three-dimensional (3D) or intensity-modulated SBRT for Stage I NSCLC or metastasis to the lung in the Department of Radiation Oncology at the University of Arizona. “Centrally located” is defined as the area within 2 cm of the proximal bronchial tree, which includes the lower trachea, carina, mainstem bronchi, and the lobar bronchi. The critical structures are the esophagus, the heart, the spinal cord, major vessels, and the major airways just described. The tumor location, size, and its distance to the immediately adjacent normal structure, as well as the critical structures at risk are listed in Table 1.

**Target volume delineation**

The gross tumor volume (GTV) was delineated at the lung window level on the treatment planning CT. The clinical target volume (CTV) was defined as the GTV and the adjacent areas that were at a high risk for microscopic tumor extension. The planning target volume (PTV) was the CTV with a 5-mm expansion to account for setup errors and tumor motion. Tumor histology was taken into consideration when the PTV was contoured except when the GTV is adherent to critical structures. In the latter situation, we believe that the dose gradient inherent to tomotherapy may provide adequate coverage for subclinical disease. The lungs, esophagus, spinal cord, and the heart were contoured for each patient. The major vessels and major airways were contoured only when they are adjacent to the GTV. Target delineation was performed in the Pinnacle treatment planning system (Philips Medical Systems, Bothell, WA). Afterwards, the planning CTs and the contours were transferred into the HT Hi-Art II planning system (TomoTherapy, Madison, WI) using the Digital Imaging and Communications in Medicine RT protocol.

**SBRT treatment planning with Tomotherapy**

The HT treatment plans generated were to deliver 6 MV photons without a flattening filter. A binary multileaf collimator (MLC) with a leaf width that projects to a 6.25 mm width at the isocenter, which is 85 cm away from the X-ray photon source, provides the intensity modulation. In the plans, longitudinal aperture sizes of 1.05 cm or 2.5 cm, and a pitch of 0.3 were used. The nominal dose-rate at the isocenter was 870 cGy/min. A modulation factor of 3 was set at the beginning of the optimization process. All SBRT plans prescribed 70 Gy delivered in 10 fractions to the PTV with heterogeneity corrections using the superposition-convolution algorithm. All plans were optimized to have at least 95% of the PTV receiving 70 Gy. The dose volume constraints used at our institution (Table 2) are derived from those used in the Radiation Therapy Oncology Group 0236 and those from previously published studies (3, 18). The linear-quadratic formulism was used in dose conversions in the generation of our current set of dose constraints, using α/β = 3.

**QA of SBRT plans**

The dosimetric accuracy of the treatment plans was determined using an A1SL ion chamber (Exradin, Middleton, WI; 0.06 cc in volume) as well as EDR-2 films (Kodak, Rochester, NY) embedded inside the Tomo-Phantom (TomoTherapy) in measuring the radiation dose and relative treatment position directly in the intensity-modulated radiation fields. Acceptance criteria for ion chamber measurements were within 5% compared with the treatment plan. A gamma analysis with the local dose difference and distance-to-agreement criteria of 3% and 3 mm, respectively, was performed.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Location</th>
<th>Size of the tumor (cm)</th>
<th>PTV volume (mL)</th>
<th>Adjacent critical structure</th>
<th>Distance to critical structure (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LUL</td>
<td>3.60</td>
<td>37.03</td>
<td>Aortic arch; left pulm artery</td>
<td>0.38</td>
</tr>
<tr>
<td>2</td>
<td>LUL</td>
<td>3.30</td>
<td>41.71</td>
<td>Aortic arch</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>RLL</td>
<td>4.60</td>
<td>54.76</td>
<td>Aortic arch</td>
<td>0.38</td>
</tr>
<tr>
<td>4</td>
<td>LUL</td>
<td>6.67</td>
<td>153.68</td>
<td>Heart</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>LUL</td>
<td>5.30</td>
<td>62.59</td>
<td>Left pulm artery</td>
<td>0.56</td>
</tr>
<tr>
<td>6</td>
<td>LUL</td>
<td>5.30</td>
<td>70.54</td>
<td>Left pulm artery</td>
<td>0.40</td>
</tr>
<tr>
<td>7</td>
<td>RML</td>
<td>3.81</td>
<td>69.22</td>
<td>SVC, right pulm artery</td>
<td>0.37</td>
</tr>
<tr>
<td>8</td>
<td>LLL</td>
<td>2.87</td>
<td>33.18</td>
<td>Heart</td>
<td>0.85</td>
</tr>
<tr>
<td>9</td>
<td>RML</td>
<td>6.31</td>
<td>147.72</td>
<td>Right pulm artery; right mainstem bronchus</td>
<td>0.49</td>
</tr>
<tr>
<td>10</td>
<td>LUL</td>
<td>2.18</td>
<td>15.9</td>
<td>Aortic arch</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**Abbreviations:** LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; pulm = pulmonary; SVC = superior vena cava.
to compare the film measurements with the calculated dose distributions of the treatment plans on the phantom. Area with gamma value of greater than 1 was considered not meeting the criteria of film analysis.

RESULTS

All treatment plans satisfied the dose constraints outlined in Table 2, as well as the PTV coverage criteria of \( \geq 95\% \) of the PTV receiving 70 Gy (Table 3). Figure 1 demonstrates the dose distribution for a tumor, for which the PTV is only 0.38 cm away from the aortic arch. As shown, the 49 Gy isodose line clearly stays off the aortic arch in such a short distance from the PTV. At the same time, the PTV is completely enclosed in the 70 Gy isodose line. The associated DVH demonstrates that the dose constraints for all the OARs were satisfied for this SBRT plan.

Dose to the lungs

The dose to the lungs is evaluated through the radiation dose to the total lung. The total lung is defined as the sum of the volumes of the left and right lung minus that of the GTV. Radiation dose to the ipsilateral and contralateral lungs were recorded as well to investigate TomoTherapy’s ability to spare the contralateral lung. The commonly used parameters of MLD, \( V_{5} \), \( V_{10} \), and \( V_{20} \) are listed in Table 4. All these parameters for the contralateral lung were significantly lower than those for the ipsilateral lung (\( p < 0.5 \)). After dose conversion with the linear quadratic equation using an \( \alpha/\beta \) of 3, the volume receiving doses biologically equivalent to 5 Gy, 10 Gy, and 20 Gy delivered with the 12.5 Gy \( \times 4 \) schedule were 17.88 \( \pm \) 2.85\%, 14.00 \( \pm \) 2.94\%, and 8.62 \( \pm \) 3.22\%, respectively, which were below those reported in previous studies on SBRT for centrally located lesions (3).

Dose to the OARs other than the lungs

The maximum dose received by the spinal cord, the esophagus, the heart, the major airways, and the major vessels is summarized in Table 5. Among them, the heart, major airways, and the major vessels, are often immediately adjacent to the PTV as illustrated in Table 1. However, the maximum dose to each structure has met the dose constraints for all patients.

Dose falloff with distance

Significant dose gradient has achieved between the PTV periphery and the immediately adjacent structure. As shown in Fig. 2, the dose fall ranged from 29\% to 82\%. Among the 10 patients, the average dose falloff was 47.6\% over an average distance of 4.87 mm from the PTV periphery to the edge of the immediately adjacent critical structure.

QA of SBRT plans

The calculated doses agreed with the doses measured by ion chamber very well. All 10 cases met the criteria for acceptance. The point dose error ranged from -1.29\% to 4.36\%, which averaged to a 1.85\% variation from the measured dose. The planned and measured two-dimensional dose distributions agreed very well with each other. The average mean gamma and the area with a gamma larger than 1, were 0.20 and 0.94\%, respectively. Figure 3 shows an example of the gamma analysis results with limits of 3 mm/3\%.

DISCUSSION

To our knowledge, this is the first study describing the dosimetric feasibility of SBRT delivered with HT for centrally located lesions. As described in previous studies, central location and proximity to critical organs have frequently been associated with severe toxicities after SBRT for early-stage NSCLC and lung metastases (4, 6, 7, 19–21). In the initial report of the Indiana University Phase II study, Grade 5 toxicity at least partially due to SBRT was observed in 6 patients (6). Four of the 6 patients had centrally located lesions. Among the Grade 5 toxicities observed, deaths resulting from pericardial effusion and massive hemoptysis occurred late at 13.8 and 19.5 months after SBRT, respectively. Both cases had tumors adjacent the major airways. On further analysis, the rate of severe toxicity (Grade 3–5 toxicity) was much higher for patients with centrally located lesions.
lesions comparing with that for patients with peripheral lesions (54% vs. 83%, $p = 0.004$). In fact, central location was associated with an 11-fold increase in the risk of severe toxicity compared with more peripheral locations. After a median follow-up of 50.2 months, a trend toward increased severe toxicity in centrally located lesions was still observed despite the small size of this study (27.3% vs. 10.4%, $p = 0.088$) (7). In another study by Le et al., Grade 5 toxicity was also frequently observed in centrally located lesions (radiation pneumonitis and tracheoesophageal fistula-related fatal hemoptysis) after 25 Gy was delivered in one fraction (19). With a lower fractional dose, severe pulmonary toxicities due to complete or partial bronchial strictures and related bleeding were still observed in tumors adjacent to the mainstem or lobar bronchi after 40–48 Gy/4 fractions or 60 Gy/10 fractions were delivered (20, 21).

![Isodose distribution](image)

**Fig. 1.** The isodose distribution for the non–small-cell lung cancer lesion immediately adjacent to the aortic arch. The axial, coronal, and sagittal views with isodose distribution are demonstrated; the isodose levels are listed on the right of the planning computed tomography (CT) images in absolute doses (Gy). The dose–volume histogram is demonstrated below the CT images, and the color for each structure is illustrated as above. GTV = gross tumor volume; PTV = planning target volume.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Maximum dose received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord (SD)</td>
<td>18.20 (8.05)</td>
</tr>
<tr>
<td>Esophagus (SD)</td>
<td>12.56 (5.27)</td>
</tr>
<tr>
<td>Heart (SD)</td>
<td>18.89 (22.49)</td>
</tr>
<tr>
<td>Major airway (SD)</td>
<td>24.27 (13.21)</td>
</tr>
<tr>
<td>Major vessels (SD)</td>
<td>43.26 (5.09)</td>
</tr>
</tbody>
</table>

**Abbreviation:** SD = standard deviation.

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Table 4. Dose to the normal lung tissue in tomotherapy SBRT plans

<table>
<thead>
<tr>
<th></th>
<th>Total lung</th>
<th>Ipsilateral lung</th>
<th>Contralateral lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD (SD)</td>
<td>7.15 (1.44)</td>
<td>12.78 (2.53)</td>
<td>1.62 (0.46)</td>
</tr>
<tr>
<td>$V_5$ (SD)</td>
<td>21.81 (2.11)</td>
<td>40.11 (5.76)</td>
<td>5.87 (3.69)</td>
</tr>
<tr>
<td>$V_{10}$ (SD)</td>
<td>16.21 (2.97)</td>
<td>34.08 (5.10)</td>
<td>0.73 (0.60)</td>
</tr>
<tr>
<td>$V_{20}$ (SD)</td>
<td>11.93 (3.24)</td>
<td>25.06 (5.78)</td>
<td>0.06 (0.10)</td>
</tr>
</tbody>
</table>

**Abbreviations:** MLD = mean lung dose; $V_5$, $V_{10}$, $V_{20}$ = % volume receiving 5 Gy, 10 Gy, and 20 Gy, respectively; SD = standard deviation.
severe toxicity was observed when a critical structure other than the major airway is very close to the tumor target volume. In the study by Onimaru et al., a patient died as a result of bleeding from an esophageal ulcer 5 months after 48 Gy/8 fractions was delivered to a 3.5 cm central lesion (4). The esophagus was included in the 80% isodose volume. On retrospective review, the maximum dose to the esophagus was 50.5 Gy, and the high dose given to 1 mL of the esophagus was 42.5 Gy. Despite the variation in dose per fraction and the total BED to the tumor target in these studies, a strong correlation between central location and severe toxicity after SBRT seems to be evident. Therefore, it is of pertinent importance to spare the major critical thoracic structures in the treatment planning of SBRT for centrally located lesions.

HT, a modality that delivers image-guided intensity-modulated fan beam in a helical fashion, has been consistently shown to improve the sparing of adjacent critical organs when compared to linac-based IMRT systems (13–15, 22). In the sparing of parotid glands, which are immediately adjacent to the PTV in the head and neck area, HT plans have been shown to decrease the normal tissue complication probability for the parotid glands by 80% when compared with linac-based IMRT plans for oropharyngeal cancer (13). With stringent dose constraints, HT plans were not only able to maintain excellent dose homogeneity within the PTV, but also decrease doses to multiple adjacent OARs in the head-and-neck region, such as the spinal cord, parotid glands, and the mandible (22). Similar patterns of improved normal tissue sparing was found in the thorax when HT plans were compared with 3D conformal and linac-based IMRT plans for locally advanced NSCLC and esophageal cancers with elective nodal irradiation omitted (15, 23–25). Despite concerns of low-dose spread through the normal lung tissue from the intrinsic nature of HT radiation delivery, the MLD from HT plans has been consistently shown to be decreased when compared with 3D conformal plans (23, 24). Clinically, dose escalation with HT in the treatment of primary NSCLC or metastases to the lung was found to be feasible in several studies. In a prospective study on the clinical feasibility of HT in the treatment of Stage III NSCLC, 16% maximally Grade 3 late toxicity (lung toxicity exclusively) was observed after 70.5 Gy was delivered in 30 fractions (26). Despite two deaths within 90 days after the start of radiotherapy from pulmonary toxicity, the acute and late toxicity profile was mostly acceptable when the MLD was kept to <18 Gy and the V20 was kept to <32%. However, no more than Grade 2 pneumonitis was observed when radiation dose was escalated to 80.5 Gy in 25 fractions with HT based on the MLD and the risk of causing Grade 2 pneumonitis in a dose escalation study for mostly Stage II-III NSCLC (27). After HT SBRT of 60 Gy delivered in five fractions for peripheral NSCLC, no ≥Grade 2 late pulmonary toxicity was encountered when the MLD was kept to <18.5 Gy/3 (equivalent dose of 2 Gy per fraction with α/β = 3) (16). When the MLD was kept below 25 Gy in patients with adequate PFT’s and below 15 Gy in patients with poor pulmonary function, no >Grade 2 pulmonary toxicity was observed after 40–50 Gy was delivered in 10 fractions through HT for up to 10 metastatic lung lesions (17).

The observed dosimetric advantages over linac-based IMRT plans seem to attribute to the fact that 51 individual intensity modulation patterns can be generated over a single gantry rotation through 51 equally spaced projections with HT, thus allowing a high degree of conformal dose avoidance in regions of complex geometry (11). Although the inclusion of the helical pitch (distance of couch movement for one gantry rotation relative to the axial beam width at the isocenter) further enhances intensity modulation by allowing multiple intensity levels for each target voxel. Therefore, significant normal tissue sparing can be achieved through HT’s unique ability for intensity modulation. This is essential for the safe delivery of SBRT in centrally located lung
lesions, especially when the PTV is immediately next (<1 cm) to a critical organ, and a large dose gradient is required to avoid potentially fatal toxicities. Thus we conduct this study to investigate the feasibility of SBRT delivered through HT in such unique situations.

In this study, dose constraints for all the critical structures were met, whereas our dose coverage criteria of ≥95% of the PTV receiving 100% of the prescription dose (70 Gy) was satisfied for all cases (Tables 3, 4, 5). Through intensity modulation with HT, a 47.6% dose reduction over a distance of 4.87 mm was achieved on average. This supports the feasibility of delivering SBRT for centrally located lesions with HT, especially in situations where the PTV is less than 1 cm from one or more critical normal structures (Fig. 1). When compared with the adopted dose constraints for normal lung for a schedule of 12.5 Gy × 4 fractions, the % total lung volume receiving doses biologically equivalent to 5 Gy, 10 Gy, and 20 Gy delivered with the 50 Gy/4 fraction regimen were below the previously reported dose constraints which was associated with no Grade 3 clinical pneumonitis after SBRT for centrally located lesions (3). In fact, only 1 case of maximally Grade 3 pneumonitis (2.3%) was observed when the V20 was kept to <20% for a cohort of patients treated with 70 Gy delivered in 10 fractions to the GTV (28). In our study, the V20 for the total lung was 11.93 ± 3.24%, which is well below 20%. The MLD for the total lung was 14.3 Gy3 on average, and <19 Gy3 for all cases which seems to correlate with a low risk for severe pneumonitis as demonstrated in multiple studies (16, 29). In addition, the dose to the contralateral lung was significantly lower than that for the ipsilateral lung (<0.05). Therefore, HT SBRT plans are able to keep the doses to the immediately adjacent structures and the normal lung tissue, especially the contralateral lung to a reasonably low level. Evidently, the high degree of intensity modulation in areas of complex geometry through HT is able to generate a sharp dose fall off to spare the immediately adjacent critical structures and the normal lungs while still satisfy the dose coverage criteria of the tumor target volume in the delivery of SBRT for centrally located lesions.

Extensive QA was performed to validate the dosimetric accuracy of each plan. All plans passed our clinical QA criteria. Ion chamber measurements have demonstrated on average a 1.85% point dose error. The planned and measured two-dimensional dose distributions highly approximate each other with a mean gamma of 0.2. Thus, all plans were validated to be highly accurate and physically deliverable for actual SBRT treatments.

There are limitations to our study that still need to be addressed in the setting of a prospective clinical study. For instance, respiratory gating or tumor tracking systems are not currently compatible with HT systems. Therefore, accurate immobilization and four-dimensional CT simulation, which can better account for internal tumor motion throughout all phases of the respiratory cycle, are essential in minimizing tumor motion. In addition, the delivery of a complex treatment plan with sophisticated intensity modulation can take a long time (up to 40 min). This obstacle may be overcome with the addition of new features, such as dynamic jaws and dynamic couch, to the next generation of HT systems to decrease the treatment time by varying the fan beam width and the speed of couch movement based on the varying degree of geometric complexity within the treated region (30). In addition, because of the small sample size of the study, the influence of tumor volume on dose fall off cannot be assessed and will be investigated in future prospective studies.

CONCLUSION

Our study provides evidence that the delivery of SBRT for centrally located lesions through HT is dosimetrically feasible. Intensity-modulation through HT allows the critical structures immediately adjacent to the tumor target volume to be safely spared when ablative doses are delivered to the target volume. Thorough QA of the treatment plans demonstrated a very high level of agreement between the calculated dose and the measured dose. Therefore, a prospective Phase I study is warranted.

REFERENCES


