

Image-Guided Hypofractionated Radiation Therapy with Stereotactic Boost for Inoperable Stage III Non-Small Cell Lung Cancer

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Abstract

Purpose/objective(s): To evaluate the dosimetric feasibility of a hypofractionated radiotherapy schedule for Stage III non-small cell lung cancers (NSCLC).

Materials/Methods: The study sample included 14 cases. The mean tumor burden (primary and nodal areas) was 111 cm³, range 10-424 cm³. Intended plans consist of an initial dose of 40 Gy in 10 fractions, followed by a 7 Gy x 5 boost. The clinical target volumes (CTV) consisted of PET avid areas only; the initial dose was delivered to the CTV+5 mm margin, and the boost to the CTV (no margin). At an alpha/beta ratio of 10, the tumor dose equivalent at 2 Gy per fraction of the proposed regimen is 94 Gy.

Results: Overall, only one of the 14 plans was considered unacceptable (lung and heart constraints were significantly exceeded). The spinal cord maximum constraint was met in all cases. The average spinal cord maximal dose from the actual plans was 31 Gy, range 21-38 Gy (2-Gy equivalent=32 Gy, range 18-43). The esophageal mean constraint was met in all cases; average dose 13 Gy (range 6-22). The mean heart dose was 7 Gy (range 1-33). The mean % volume of total lung-PTV receiving 15 Gy was 27% (range 17-50%). The total lung-PTV mean dose was 11 Gy (range 6-17). The tracheobronchial tree constraint (V50 Gy) was set at 15 cm³ and was met in 11 of the 14 cases; three cases marginally exceeded the limit. The brachial plexus was relevant for three patients, with an average V45 Gy of 0.6 cm³ (range 0-8.)

Conclusions: This study demonstrates the dosimetric feasibility of an aggressive hypofractionated regimen for Stage III lung cancer patients.

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Categories: Radiation Oncology

Keywords: non-small cell lung cancers (nsclc), lung cancer, hypofractionated radiotherapy, adaptive radiotherapy, dosimetric planning

Introduction

Current treatment for patients with inoperable Stage II and III NSCLC consists of concurrent chemotherapy and radiation treatment. However, the five-year survival rate is a dismal 15-20%

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[1], with rates of locoregional failure and distant relapse of approximately 50% [2-4]. With the success of stereotactic body radiotherapy (SBRT) in treating Stage I NSCLC [6], it is reasonable to assume that a similar treatment approach may also be successful for locally advanced NSCLC. Since locally advanced lung cancer is often centrally located and occupies a significantly larger volume, treatment schedules need to be more fractionated than a typical Stage I lung cancer SBRT schedule to respect the normal tissue. Such schedules should still deliver doses in the order of 100 Gy to areas of gross involvement, based on equivalent doses in 2 Gy (EQD2) estimations and biological effective dose modeling. Efforts should be taken to decrease the volume of normal tissues irradiated to such large fraction sizes, possibly via adaptive radiation therapy. Re-imaging after irradiation to a certain level allows for treatment fields to be adjusted to the shrinking tumor volumes—thus avoiding unnecessary irradiation of normal tissue at the highest doses. This approach, although promising, still lacks robust evidence of efficacy, is one strategy to decrease the treatment volume while still escalating the dose. Aggressively targeting metabolically active areas may result in improved outcomes. For example, a complete metabolic response by PET in patients with locally advanced NSCLC was associated with an improvement in median survival from 11 months to 31 months, and reduction in local failure by more than 50% [6].

A Phase I dose-escalation clinical trial is currently being implemented at UCLA testing the safety and efficacy of a hypofractionated regimen of 4 Gy x 10, with a dose escalated adaptive boost. The adaptive boost doses to be tested range from 25 to 35 Gy in five fractions. The initial cohort of the clinical trial will be treated to a total dose of 65 Gy in 15 fractions. The EQD2 (equivalent dose in 2 Gy) for this cohort is calculated to be approximately 78 Gy (a reasonable dose to start given the current understanding of thoracic organ dose tolerances). The current analysis is a dosimetric feasibility study of the highest doses planned for the clinical trial. This regimen consists of 4 Gy x 10, followed by 7 Gy x 5, for a total nominal dose 75 Gy delivered in 15 fractions. The clinical trial will include re-imaging with a CT-PET near the end of first 10 fractions, followed by the adaptive boost. This dosimetric study assumes the worse case dosimetric scenario for the normal tissue, presuming no disease response upon re-imaging. This is to ensure that the worse case scenario, without tumor shrinkage, still meets reasonable normal tissue dose constraints prior to enrolling such a patient. Dosimetry of the intended target and normal tissues are analyzed in the context of extrapolated normal tissue dose constraints.

Materials And Methods

Planning

The study was performed using CT and pre-treatment FDG-PET scans from 14 patients with histologically confirmed primary non-metastatic Stage III NSCLC. The group average age was 67 years, with seven male and seven female patients. There was an average of 2.3 sites of disease per patient (range 1-4), with an average maximum primary tumor diameter of 4.7 cm (range 0.9-10.3). As part of their treatment simulation, a standard CT scan and a 4DCT scan were acquired. Patients were scanned with a Siemens Sensation Open (20 slice) CT scanner and 4DCT acquisition acquired with the Anzai respiratory monitor system (AZ-733V, Anzai Medical, Tokyo, Japan). The 4DCT scan, performed under normal free-breathing conditions, was reconstructed at three respiratory phase points: full exhale, mid-inhale, and full inhale.

The esophagus, proximal tracheal/bronchial tree, heart, and brachial plexus (when dosimetrically relevant) were contoured (CH, PK, and PL). The normal lung, spinal cord, and body were delineated using auto-contouring tools available in the treatment planning system. The lung, excluding PTV, and skin contours were generated using Boolean operators. These organs were designated as the organs at risk (OAR). The gross tumor volume (GTV) were defined based on the PET scan to aid gross tumor segmentation, and expanded to include tumor motion

based on the 4DCT to form the internal target volume (ITV). A 5 mm margin expansion of each ITV yielded the initial planning target volume (PTV) for the first 10 fractions. The goal and rationale for small margin is to tightly conform the dose to the target accounting for motion, minimize unnecessary spillage to organs at risk with care to use daily volumetric image-guidance (cone-beam CT) to ensure accuracy. Also, given the hypofractionated nature, the dose in this 5 mm margin is greater than that from a standard 2 Gy fraction regimen and may be more effective in sterilizing microscopic disease. Assuming no response, the treatment volumes from the initial CT and PET scans were maintained for the initial and boost phases. However, for the boost portions of the plan (last five fractions), the PTV was equivalent to the ITV since no additional margin was used for the boosts, ensuring volume reduction for the boost.

The radiation treatment plans were generated using the Varian Eclipse treatment planning system and planned with multiple (generally more than nine) fields intensity modulated radiotherapy (IMRT) technique. All planned treatments consisted of an initial dose of 40 Gy in 10 fractions (4 Gy x 10), followed by a 7 Gy x 5 boost. Plans consisted of nine co-planar non-opposing photon beams of 6 MV-energy. The dose calculation algorithm used was the Varian Anisotropic Analytic Algorithm Version 8.6.14 (AAA) with heterogeneity correction. All plans were normalized to deliver the prescribed dose to at least 95% of the PTV. The following total equivalent-dose constraints were used for normal tissues: 1) spinal cord maximal point dose <45 Gy, 2) esophagus mean dose < 25 Gy, heart mean dose < 25 Gy, 3) total lung-PTV V15 Gy < 40% and mean lung dose < 15 Gy, 4) tracheal/bronchial tree V50 Gy < 15 cm³, 5) skin V50 Gy < 5 cm³, and 6) if relevant, brachial plexus V45 Gy < 5 cm³. Dosimetric statistics generated from the treatment plans were subsequently analyzed.

Dose equivalences

The study comprises of 15 total treatments, divided into 10 4 Gy fractions and five 7 Gy fractions. To simplify calculation and make a fair estimate, it was assumed the average fraction size is 5 Gy. However, this represents the dose to cover 95% of the PTV and not the dose at individual OARs. In modern radiotherapy, with small volume targets and sharp dose fall-offs, normal tissue constraints should be individually considered, rather than based on the prescription target doses [7]. These would typically be much less due to the rapid dose fall-off achievable with current planning and delivery techniques. In order to calculate the per fraction dose at each OAR in each individual patient, we utilized the dose statistics generated by each treatment plan. For example, in Patient 3 (see Figure 4), the spinal cord maximum dose is 30 Gy. Divided by 15 fractions, the spinal cord is receiving at maximally 2 Gy per fraction. Dosimetric constraints and measured parameters were set based on experience with the conventional treatment fractionation of 2.0 Gy/fraction (Table 2).

Patient set-up and immobilization

For the clinical trial, patients will be immobilized with a whole body VacLock™ (CIVCO Medical Solutions, Kalona, Iowa), while stabilizing patients' arms above their head. PET-CT scans will be performed with intravenous iodine-based contrast, with slice thickness of 2 mm in the region of interest. Daily imaging with volumetric KV Cone Beam CT will be performed for all 15 fractions. After planning, phantom-based quality assurance will be performed on the initial 10 fractions, as well as the adaptive boost treatment plans.

Results

Locations of the tumors were categorized by dividing the thorax into three equal portions in the coronal plane (peripheral right, central, and peripheral left) and transversally at the carina to distinguish upper from lower (Table 1) [8]. Distribution of the primary lesions is shown in

Figure 1. Involved lymph nodes (based on tumor anatomy on CT) were categorized according to the regional lymph node stations for lung cancer staging [9]. The number of lesions at each nodal station is indicated in parenthesis: nodal station 2 (1), nodal station 7 (1), nodal station 10 (9), nodal station 11 (9), nodal station 12 (4), nodal station 13 (3), and nodal station 14 (3).

Patient	Primary lesion location	Primary lesion diameter (cm)	Node location(s)	Nodal diameter(s) (cm)	Total volume (cm3)
1	RUC	3.2	10-11	4.7	79
2	RUC	3.1	10-11	3.6	41.3
3	RUC	4.4	2,10-11	1.5, 2.8	22.3
4	RLP	5.5	10-11	1.5, 2.2, 4.6	34.7
5	RUC	8.2	10-12	0.9, 2.0, 2.5	125.4
6	RUC	2.4	10-11	11	424.3
7	RUC	1.5	7, 10-14	1.5, 2.0, 2.4	17.2
8	LLP	8.5	None	None	148.7
9	LUC	5.5	None	None	110.7
10	LUC	3.6	10-14	1.1	31.4
11	RLP	10.3	10-12	2.1	330.8
12	RUP	1.9	13-14	2.5	9.7
13	RUP	9.3	None	None	88.4
14	LUC	7.1	None	None	92.2

TABLE 1: Patient and tumor characteristics

Primary lesion location classification is classified as right vs. left, upper vs. lower, and central vs. periphery lesions. For example, RUC refers to a lesion in the right upper central area of the lung. The node location classification is according to the classification per lung cancer nodal staging, and is depicted in Figure 2.

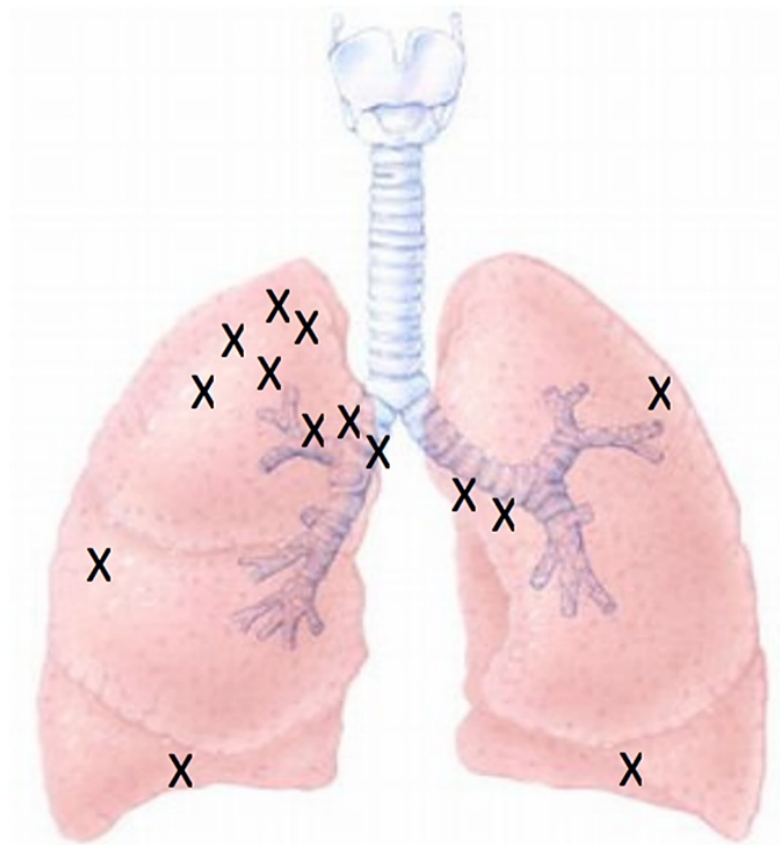


FIGURE 1: Distribution of primary lesions.

There was no difficulty in meeting the spinal cord maximum constraint in all patients. The average spinal cord maximal dose from the actual plans was 31 Gy, range 21-38 Gy (2-Gy equivalent=32 Gy, range 18-43). The esophageal mean constraint was met in all patients, with an average dose of 13 Gy (range 6-22 Gy). The heart mean dose was achieved for all but one patient, with a mean heart dose of 7 Gy (range 1-33 Gy). The mean V20 Gy of the normal lung (Total lung - PTV) was 27% (range 17-50%). Total lung - PTV mean dose were met for all but one patient, average of 11 Gy (range 6-17 Gy). The average and extreme cases of the dose-volume-histogram for the lung and esophagus are depicted in Figure 2. Note that the same patient (Patient 6) failed to meet heart and lung constraints. The skin V50 Gy was negligible overall. The tracheobronchial tree constraint was met for 11 of the patients, with an average V50 Gy of 9 cm³ (range 1- 21 cm³). The constraint was marginally exceeded in three patients with 19, 20, and 21 cm³. The brachial plexus was relevant for three patients, with an average V45 Gy of 0.6 cm³ (range 0-8 cm³). Table 2 details the dose constraints of each OAR in the 14 patients, and unmet constraints are in bold. Figure 3 demonstrates a representative patient (Patient 3) in which both the target coverage and normal tissue goals were achieved on cross-sectional imaging.

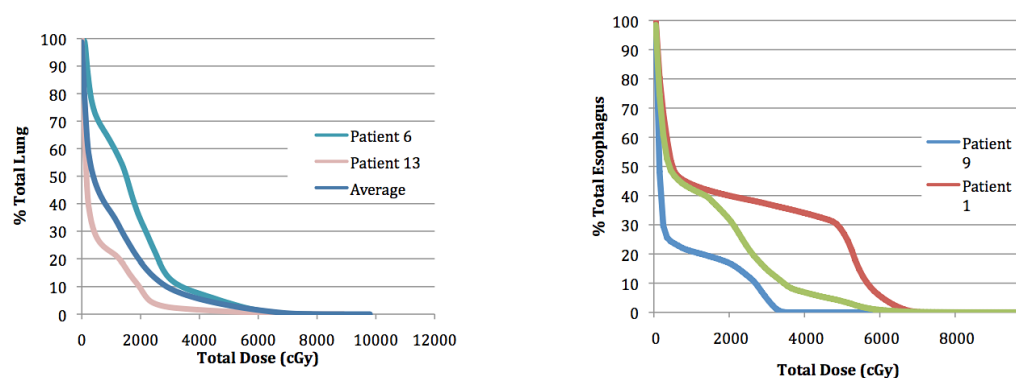


FIGURE 2: Data Visualizations

A) DVH of Lung - PTV in patients with the lowest and highest V20. Average of all 14 patients is also displayed. B) DVH of esophagus for patients with the lowest and highest mean values, and average of all 14 patients.

Patient	Spinal cord max. dose (Gy)	Esophagus mean dose (Gy)	Heart mean dose (Gy)	Total lung-PTV V15 Gy (%)	Total lung- PTV mean (Gy)	Skin V50 Gy (cm ³)	Tracheal/bronchial tree V50 Gy (cm)	Brachial plexus V45Gy (cm)
2 Gy equivalent constraint	<45	<25	<25	<40	<15	<5	<15	<5
1	33 (35)	22 (19)	2 (1)	31	12 (8)	0	19	None
2	26 (24)	13 (9)	1 (1)	24	10 (7)	0	6	0
3	30 (30)	10 (7)	1 (1)	23	8 (5)	0	10	None
4	28 (27)	15 (11)	12 (8)	34	14 (10)	0	10	None
5	35 (38)	17 (13)	2 (1)	34	14 (10)	0	20	8
6	38 (43)	17 (13)	33 (35)	50	17 (13)	0	10	None
7	31 (32)	13 (9)	9 (6)	26	11 (8)	0	4	None
8	27 (26)	16 (12)	15 (11)	23	11 (8)	0	0	None
9	28 (27)	6 (4)	1 (1)	22	10 (7)	0	1	None
10	21 (18)	10 (7)	12 (8)	21	10 (7)	0	5	None
11	29 (29)	16 (12)	4 (2)	38	14 (10)	0	21	None
12	33 (35)	7 (4)	1 (1)	18	9 (6)	0	7	None
13	37 (41)	12 (8)	1 (1)	17	6 (4)	0	1	1
14	38 (43)	11 (8)	2 (1)	21	9 (6)	0	12	None

TABLE 2: Dosimetry statistics using biologically equivalent doses (derived via the linear quadratic model)

Constraints were derived from known acceptable doses at standard 1.8-2.0 Gy fractionation. Each cell lists two numbers: 1) the value generated by the plan, and 2) in parentheses, the 2-Gy dose equivalent doses.

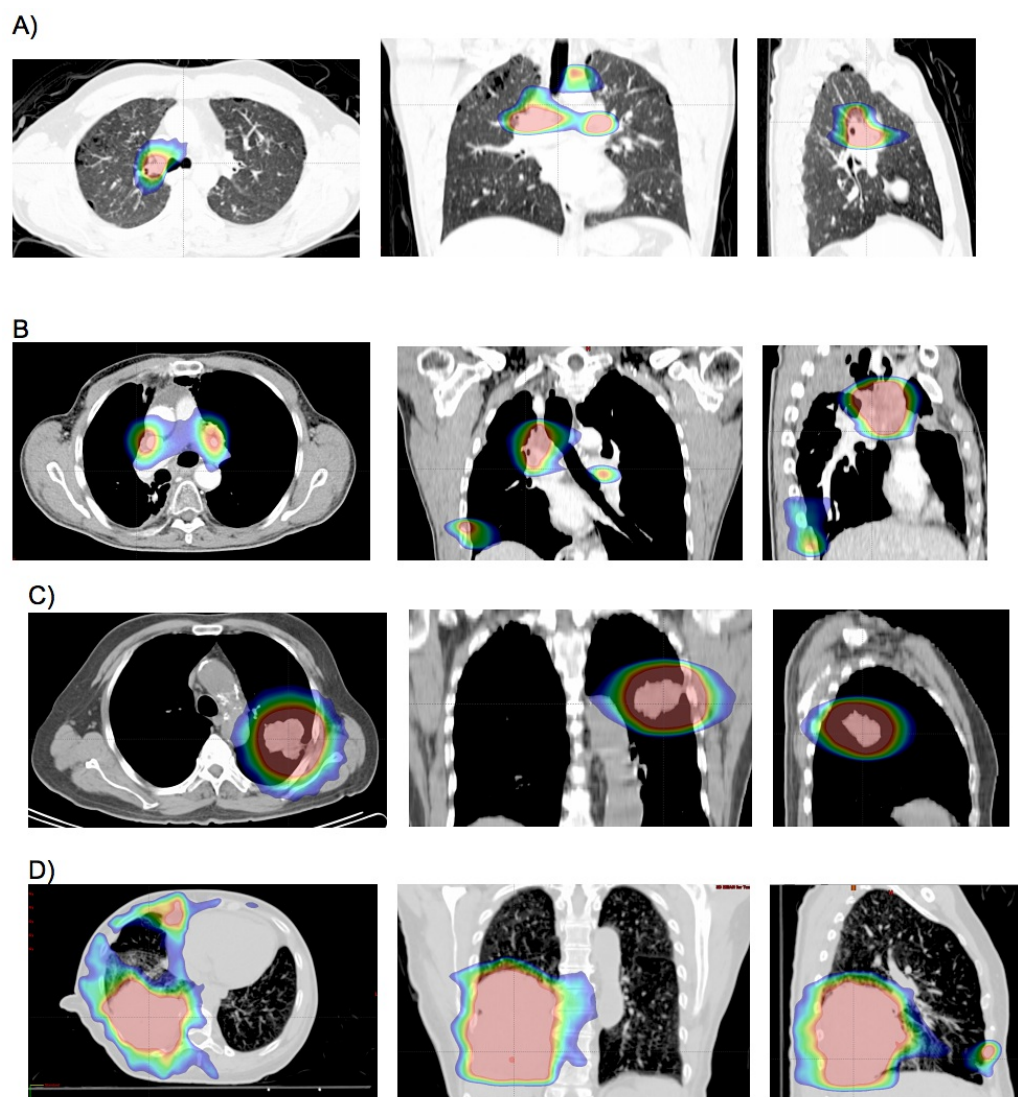


FIGURE 3: Sample treatment plan

Sample treatment plan sums (initial plus boost plan) are shown in absolute dose color wash. Fig. 3D shows treatment plan for patient who did not meet the heart and lung dose constraints. A) Patient 3, B) Patient 4, C) Patient 9, D) Patient 6.

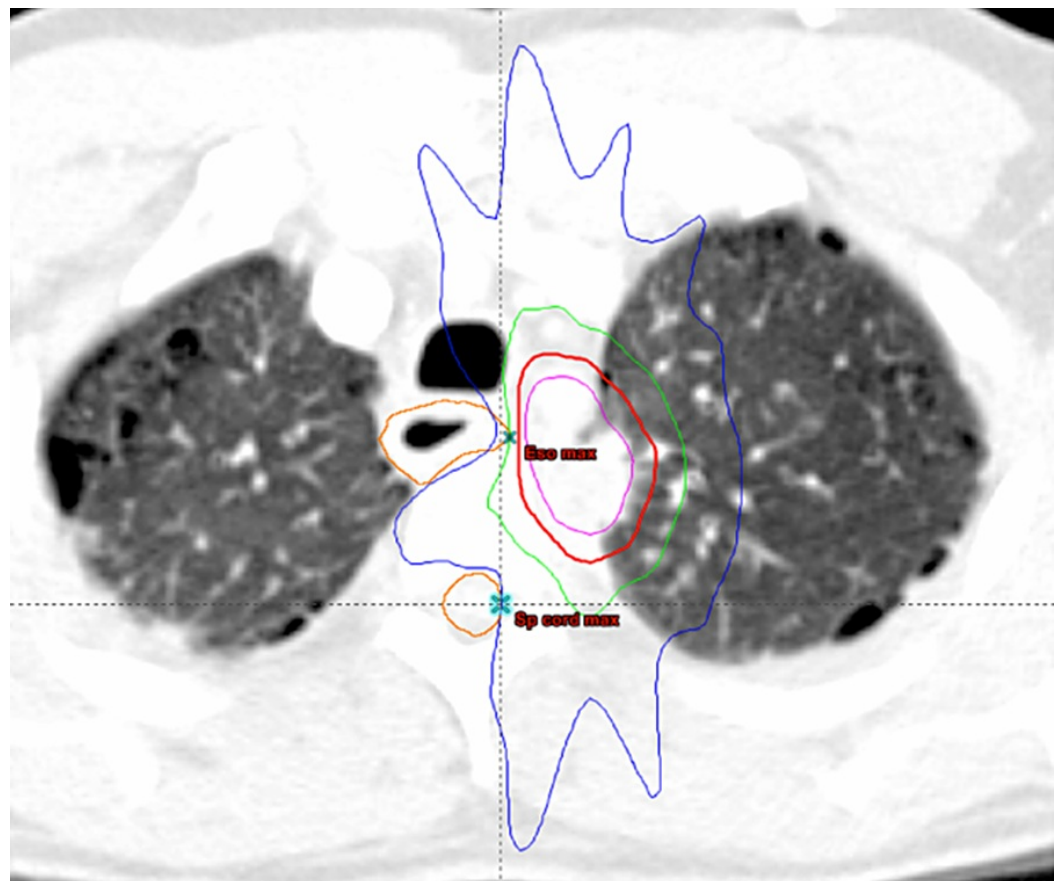


FIGURE 4: Dose plan for Patient #3

Discussion

When discovered early, Stage I NSCLC (no lymph node involvement) surgical and non-surgical treatment options offer a 50-70% five year overall survival rate. In contrast, the five year overall survival for patients with inoperable Stage II and III NSCLC is disappointing, with an estimated five year survival rate of 15-20% [1]. Rates of locoregional failure after chemoradiotherapy can be as high as 50%, and distant relapse after chemoradiation therapy can be greater than 50% [2-4]. One potential possibility for such high rates of distant relapse may be the failure to achieve local tumor control with the standard doses and fractionation schemes currently used (60-74 Gy, delivered in 1.8-2.0 Gy per fraction) [10]. Furthermore, in RTOG 0617, which randomized locally advanced NSCLC patients to receiving cetuximab and 60 versus 74 Gy, the two arms containing 74 Gy were closed prematurely due to an interim futility analysis that showed that the survival in the 74 Gy arm was no better than that of the 60 Gy arm (Bradley, et al., ASTRO Annual meeting 2011, Miami FL). Therefore, traditional dose-escalation using conventional fraction size is unlikely to improve outcomes in locally advanced lung cancer. The meta-analysis by the NSCLC Collaborative Group substantiated the importance of local regional tumor control: the comparison of concurrent chemoradiotherapy versus sequential chemotherapy and radiation therapy revealed an improved overall survival for concurrent treatment (HR=0.84), attributed to less locoregional progression (HR=0.77) [11]. As such, the current protocol at UCLA for this hypofractionated regimen consists of mandatory concurrent weekly carboplatin and paclitaxel with radiation during the three week regimen, followed by the option of adjuvant systemic therapy at the oncologist's discretion. Recent trials of SBRT in Stage I NSCLC suggest that a hypofractionated regimen of high nominal doses can dramatically increase local tumor control. Studies using three to five fractions of high doses (12-26 Gy per

fraction) achieved excellent local tumor control, exceeding 90% [5, 12-14] with low rates of complications. Studies of different radiation-fractionation dose schedules have indicated that repopulation of cancer cells often has a dominant effect on treatment outcome [9]. Hypofractionation facilitates shorter treatment times, thus allowing less opportunity for repopulation and decreasing the possibility of a treatment break. Hypofractionation may even have a beneficial impact on normal tissue toxicities given the associated small volume irradiation leading to small volumes and doses in relevant OARs [7-8].

Data [8] suggest that an improvement in locoregional control with newer, more innovative forms of radiation therapy may translate into further improvement in five year survival. Current radiation therapy delivered at 1.8-2.0 Gy per fraction is limited by the relatively high radiosensitivity of the normal lung and tissue, and the large margins typically used for treatment. However, a 2010 study by Timmerman, et al. of SBRT in early stage lung cancers showed an impressive three year survival at 56% with a relatively low rate of toxicity (13% and 4% of patients reported protocol-specified treatment-related Grade 3 and 4 adverse effects, and an additional 11% unclassified adverse events) [5] for medically inoperable patients. The success of SBRT in tumor control and surprisingly low-toxicity profile observed in an 18 Gy x 3 fractionation regimen raises the possibility of extending this treatment strategy to more advanced cancers. Given the larger volume of disease in locally advanced NSCLC, the fraction sizes in this study were significantly reduced to 4-7 Gy, compared to the 18-20 Gy fraction sizes used for Stage I lung cancer. By utilizing sophisticated image guidance, a higher radiation dose per fraction can be given to a smaller treatment volume in a more specific manner. Treatment volume adaptation by re-imaging throughout the treatment course will further increase the ability to focus and treat smaller target volumes. The proposed UCLA trial looks at adaptive radiation therapy after 4 Gy x 10 by modifying the boost treatment volume per an adaptive PET imaging, and boosting with a dose per fraction escalation scheme of 5, 6 and 7 Gy x 5. The actual radiation boost volumes will likely be smaller than those estimated in this current paper, given the use of the adaptive radiation therapy strategy proposed in the clinical trial. In the clinical study, all patients will undergo a repeat PET-CT, 4D CT simulation at the eighth or ninth fraction in order to identify areas of residual PET uptake to boost without having a planned treatment-break for the adaptive planning. There is an anticipated 20-30% decrease in the target volume after the initial hypofractionated therapy using this approach [15]. The current dosimetric study in 14 representative patients demonstrates that this treatment approach is feasible. Representative plans with dose color wash for Patients 3, 4, 9, and 6 are shown in Figure 3. Dose constraints were largely met, under the assumption of an approximated 5 Gy dose/fraction, calculated doses at each OAR generated by the individual plans, and the known allowable 2 Gy doses for each OAR. In the following discussion, note that Patient 6 will be discussed separately due to the plan's failure to meet the heart and lung dose constraints. In three of the 14 patients (Patients 1, 5 and 11), the dose constraints for the tracheal/proximal bronchial tree were not met. From Table 1, Patients 1 and 5 are both RUC lesions with total volumes of 79 and 125 cm³. Although the proximity of the tumor lesions to the tracheal/bronchial tree is a factor, it appears that the volume of tumor involvement is a much larger factor when we compare the volumes of these RUC lesions (17-41 cm³) to the patients that were able to meet constraints. The plan for Patient 5 also failed to meet the brachial plexus constraint of V45 Gy < 5 cm³ (8 cm³). Compared to Patient 13 (the other patient with quantifiable brachial plexus involvement at 1 cm³), Patient 5 had a significantly larger volume of involvement (125 vs. 88 cm³). The third patient (Patient 11) failing the trachea/bronchial tree constraint had a RLP lesion consisting of 331 cm³, the second largest tumor volume of the patient group. In conjunction with the lymph node stations, the target volume consisted of a large portion of the proximal bronchial tree. Patient 6 (see Figure 3D) failed to meet constraints of the heart and total lung - PTV V15 % criteria. The immense bulk of the tumor (424 cm³), roughly half of the right lung on visual inspection, makes this patient an undesirable candidate

for such an aggressive hypofractionation regimen, and would be likely excluded in the clinical trial.

Overall, there was no difficulty in meeting the spinal cord, esophagus, heart, total lung - PTV, skin, tracheal/bronchial tree, and brachial plexus constraints, except as noted above. The data revealed that in these 14 patients of varying tumor sizes and locations, the esophagus and lung - PTV fell comfortably within the constraints and the heart received at most, half of the set constraints.

The nominal dose of 75 Gy delivered over 15 fractions can seem overtly aggressive. However, the boost doses are delivered specifically to cancerous areas (defined by PET) with no margin whatsoever. Only fall-off doses will provide some dosimetric margin, while the bulk of the radiation dose is delivered to known cancer involvement. Although this study does not address delivery aspects, such as image guidance, it is clear that accurate targeting is crucial in the absence of treatment margins and reliance on fall-off dose. Our plan is to repeat in-room CT scans daily throughout the course of therapy, with frequent stereoscopic X-rays to verify the stability of patient positioning throughout the delivery.

Conclusions

In conclusion, the study showed that a regimen consisting of 4 Gy x 10 followed by a boost of 7 Gy x 5 is dosimetrically feasible in Stage III lung cancer patients. Additionally, it shows that dosing constraints can be met comfortably and those structures requiring further adjustment (e.g. tracheal/bronchial tree) will be based on individual patient anatomy. For each of the first two of three dose-escalation cohorts in the Phase I dose-escalation trial (5 Gy x 5 and 6 Gy x 5), 7-14 patients will be treated. Advancement to the next dose cohort can only occur if less than 33% of the treated patients (minimal of seven patients treated per cohort) have Grade 3 or higher acute (within 90 days of treatment) dose-limiting toxicity (upper GI, thoracic, or cardiac). Based on this dosimetric feasibility study, this dose-escalation hypofractionated radiation trial for locally advanced NSCLC has been launched at our institution.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. David Geffen School of Medicine at UCLA issued approval N/A. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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