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Basic Original Report

Full Dose SBRT in Combination With Mediastinal Chemoradiation for Locally Advanced, Non-Small Cell Lung Cancer: A Practical Guide for Planning, Dosimetric Results From a Phase 2 Study, and a Treatment Planning Guide for the Phase 3 NRG Oncology LU-008 Trial

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Purpose: Stereotactic body radiation therapy (SBRT) has been used with high effectiveness in early-stage non-small cell lung cancer (NSCLC) but has not been studied extensively in locally advanced NSCLC. We conducted a phase 2 study delivering SBRT to the primary tumor followed by conventionally fractionated chemoradiation to the involved lymph nodes for patients with node-positive locally advanced NSCLC. This manuscript serves as both a guide to planning techniques used on this trial and the subsequent phase 3 study, NRG Oncology LU-008, and to report patient dosimetry and toxicity results.

Methods and Materials: We initiated a phase 2 multicenter single arm study evaluating SBRT to the primary tumor (50-54 Gy in 3-5 fractions) followed by conventionally fractionated chemoradiation to 60 Gy in 2 Gy fractions with doublet chemotherapy to the involved lymph nodes for patients with stage III or unresectable stage II NSCLC. Patients eligible for adjuvant immunotherapy received up to 12 months of durvalumab. We report a detailed guide for the entire treatment process from computed tomography simulation through treatment planning and delivery. The dosimetric outcomes from the 60 patients who completed therapy on study are reported both for target coverage and normal structure doses. We also report correlation between radiation-related toxicities and dosimetric parameters.

Results: Sixty patients were enrolled between 2017 and 2022. Planning techniques used were primarily volumetric modulated arc therapy for SBRT to the primary tumor and conventionally fractionated radiation to the involved nodes, with a minority of cases using dynamic conformal arc technique or static dynamic multileaf collimator intensity modulated radiation therapy. Grade 2 or higher

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pneumonitis was associated with lung dose V5 Gy > 70% and grade 2 or higher pulmonary toxicity was associated with lung dose V10 Gy > 50%. Only 3 patients (5%) experienced grade 3 or higher pneumonitis. Grade 2 or higher esophagitis was associated with esophageal doses, including mean dose > 20 Gy, V60 Gy > 7%, and D1cc > 55 Gy. Only 1 patient (1.7%) experienced grade 3 esophagitis.
Conclusions: SBRT to the primary tumor followed by conventionally fractionated chemoradiation to the involved lymph nodes is feasible with planning techniques as described. Radiation-related toxicity on this phase 2 study was low. This manuscript serves as a guideline for the recently activated NRG Oncology LU-008 phase 3 trial evaluating this experimental regimen.

Introduction

Concurrent chemoradiation has been the standard-of-care therapy for stage 3 non-small cell lung cancer (NSCLC) for over 25 years, but 5-year overall survival (OS) rates have remained poor, with nearly 50% of patients having primary tumor failure with chemoradiation when radiation therapy is delivered in conventional fractionation to 60 Gy.[1] The PACIFIC regimen created a new standard of care with the addition of adjuvant durvalumab in those patients without progression after chemoradiation, with a 5-year OS rate of 42.9% and a 5-year progression-free survival rate of 33.1%.[2] Given that OS remains limited and almost 70% of patients will experience disease progression, there remains an opportunity to improve the preimmunotherapy treatment approach. Given that the primary tumor and lung were the most common sites of failure among patients treated on PACIFIC,[3] it is critical to identify newer radiation techniques that can allow for escalated dose to the primary tumor while not increasing, and potentially even decreasing, toxicity.

Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation therapy has been used as standard of care for treatment of early-stage inoperable NSCLC.[4-6] Given the local control rates seen with SBRT in early-stage NSCLC, attempts have been made to incorporate SBRT into the treatment of locally advanced (LA) NSCLC to increase primary tumor control by increasing the biologically effective dose. Given concerns of potential toxicities of high doses of radiation to central structures, SBRT has not been routinely incorporated into the treatment paradigm for unresectable LA NSCLC. Our institution conducted a phase 2 single-arm trial with 60 participants across 8 centers who were treated with full-dose SBRT in 3 to 5 fractions to the primary tumor followed by mediastinal conventionally fractionated radiation therapy to 60 Gy in 2 Gy fractions with concurrent platinum doublet chemotherapy followed by consolidative immunotherapy in patients who were eligible. Both peripherally located tumors and centrally located tumors were allowed on study, with central tumors necessitating 2 cm of separation from involved nodal metastases. This study has completed accrual, with preliminary toxicity results previously reported.[7] The preliminary efficacy results have led to approval of a randomized phase 3 study to be conducted through NRG Oncology, LU-008, that became activated internationally in 2023. This study randomized patients to standard-of-care fractionated chemoradiation to 60 Gy in 2 Gy fractions to the primary tumor and nodal metastases versus SBRT 50 to 54 Gy in 3 to 5 fractions to the primary tumor followed by conventionally fractionated chemoradiation to 60 Gy in 2 Gy fractions to the nodal metastases. Eligible patients in both arms also received consolidation immunotherapy per standard of care.

Combining full-dose SBRT and mediastinal nodal radiation creates unique dosimetric challenges, especially in patients with primary tumors in closer proximity to involved nodal metastases. The goal of this manuscript is to provide details of the planning process from computed tomography (CT) simulation through treatment delivery as a detailed guide for centers opening this upcoming landmark NRG Oncology study. We additionally report detailed dosimetry data and correlate high-grade acute toxicities to dosimetric parameters.

Methods and Materials

Patient eligibility

Patients enrolled on the phase 2 study all had pathologically proven diagnoses of stage 2 or 3 (American Joint Committee on Cancer, 8th ed) NSCLC with appropriate imaging including positron emission tomography (PET)/CT and magnetic resonance imaging of the brain with contrast (unless contraindicated) for staging workup. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 to 2 and have adequate hematologic and renal function for chemotherapy. Both weekly carboplatin/paclitaxel or 2 cycles of cisplatin/etoposide were allowed. After publication of the PACIFIC trial,[3] eligible patients went on to receive adjuvant durvalumab for up to 12 months per updated standard of care. Additional eligibility parameters included primary tumor size $\leq$ 7 cm and at least 1 nodal metastasis. For patients with centrally located primary tumors (within or touching the zone of the proximal bronchial tree), nodal disease had to be at least 2 cm from the primary tumor.

CT simulation

Patients were simulated supine with utilization of 4-dimensional CT for assessment of target and normal

Table 1 Description of target volumes

IGTVp_	IGTV primary (SBRT): Volume enveloping GTV motion of primary lung tumor over the course of the respiratory cycle
IGTVn	IGTV nodes (standard): Volume enveloping GTV motion of the involved hilar and mediastinal lymph nodes over the course of a respiratory cycle
IGTV_Combined	Combined IGTVp + IGTVn
ICTVn	ICTV nodes: IGTVn + 0.5-cm margin to account for microscopic tumor extension. Cropped to not expand into other organs such as esophagus, heart, major blood vessels, or bone unless clinically indicated
PTVp_	PTV primary (SBRT): IGTVp + 0.5-cm setup margin in all directions
PTVn	PTV nodes: ICTVn + 0.5-cm setup margin in all directions
PTV_Combined	Combined PTVp + PTVn

Abbreviations: GTV = gross tumor volume; ICTV = internal clinical target volume; IGTV = internal gross target volume; PTV = planning target volume; PTVp = primary tumor PTV; SBRT = stereotactic body radiation therapy.

tissue respiratory motion. One CT simulation was performed for both the SBRT plan and the chemoradiation plan. One CT data set was preferred to enable both plans to be calculated on the same data set and reduce the uncertainty of accumulated dose with 2 different patient setup positions. Patient immobilization typically consisted of a wing board and vac lock to immobilize at a minimum the upper torso and arms. SBRT frames with longer vac locks to include the lower torso were also used, as necessary. Patient comfort was prioritized. For patients with anticipated high magnitudes of respiratory motion (lower lobe primary tumors), abdominal compression was used to reduce respiratory motion, typically for both the SBRT and chemoradiation portions of treatment to reduce deformation between setups. Gating and breath hold were not used in this study but represent other techniques that could be applied for motion control.[8] CT slice thickness was recommended to be 2 mm or less. Anterior/Posterior (AP) and lateral scout films were taken before CT acquisition. Patients were scanned to include the entire thorax with the field of view extended to try to include the upper arms and elbows to at least 5-cm below the diaphragm to help predict collisions with gantry rotation. All patients were simulated with free breathing with 4-dimensional CT, and the representative phases, maximum intensity projection, and average intensity projection (AveIP) were transferred to the planning software.

Contouring

Table 1 contains a list of target volumes and expansion descriptions. Targets in the lung were drawn using lung windows, with soft tissue windows used as a reference to avoid inclusion of adjacent vessels or atelectasis when applicable. Staging PET/CT and CT chest with contrast were encouraged for multimodality structure definition. Deformable registration was performed when applicable using AAPM TG132 QA and commissioning procedures.[9] PET/CT was specifically useful in delineating tumor from normal tissue with similar CT appearance and for defining nodal targets that should be included.[10] Table 1 describes the target volumes created for the primary tumor and involved hilar and mediastinal lymph nodes with a description of the expansions used for clinical target volume (CTV) and planning target volume (PTV) formation, where appropriate.

Table 2 Normal structure constraints for stereotactic body radiation therapy to the primary tumor

Normal structure	3 fractions	4 fractions	5 fractions
Spinal cord	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	28 Gy (5.6 Gy/fx)
Esophagus	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	38 Gy (7.6 Gy/fx)
Brachial plexus	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Heart/pericardium	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	38 Gy (7.6 Gy/fx)
Great vessels	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	53 Gy (10.6 Gy/fx)
Trachea/proximal bronchi	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	50 Gy (10 Gy/fx)
Rib*	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	57 Gy (11.4 Gy/fx)
Skin	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	38.5 Gy (7.7 Gy/fx)
Stomach	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	35 Gy (7 Gy/fx)

Abbreviation: fx = fraction.
* Rib dose in excess of the constraints was documented but not a reason to necessitate subject withdrawal.

Table 3 Target dose coverage requirements for plan summation

PTVp	D99% (%)	≥90	≥85
	D95% (%)	≥100	≥95
PTVn	D95% (%)	≥100	≥95

Abbreviations: PTV = planning target volume; PTVn = PTV nodes; PTVp = primary tumor PTV.

Table 2 describes a list of normal tissue structures required for contouring evaluation.

Dosimetry planning

The AveIP was used for dose calculation. Target volumes were defined ideally on the same AveIP scan per the previously mentioned guidelines and are summarized in Table 1.

SBRT to the primary tumor planning

For SBRT plans to the primary tumor, all plans were with photons, and planning techniques were primarily volumetric modulated arc therapy (VMAT), as well as a dynamic conformal arc technique. VMAT arcs were typically coplanar, and most commonly 2 arcs were used with a 180° range on the ipsilateral side. Some arcs spanned >180°, but only 10.0% of cases used 360° arcs. Six MV photons were used with 6FFF allowed for SBRT plans with dose rates up to 1400 MU/min. Allowed doses for SBRT were 50 to 54 Gy in 3 to 5 fractions. For peripheral tumors with little overlap in dose with the conventionally fractionated radiation to the nodal disease, 54 Gy in 3 fractions was given to the primary tumor. For peripheral lesions where there was more appreciable overlap of dose with the conventionally fractionated radiation to the nodal disease, 50 Gy in 4 fractions was typically chosen. All central tumors received 50 Gy in 5 fractions. For the SBRT to the primary tumor plans, optimization priorities were as follows: (1) to achieve target volume coverage, (2) to meet normal structure constraints as shown in Table 2, and (3) to avoid intermediate dose overlap with the PTVn. Typically, overlap of dose was prioritized in the list of objectives to where dose falloff in that direction could be achieved assuming all other normal tissue constraints were being met. The commonly used measures of R50, D2cm, and R100 seen in primary tumor SBRT for early-stage lung cancer were not used as part of the planning process. Once these priorities were maximized, planning commenced on the conventional radiation plan to the nodal disease. An example of an individual SBRT plan to minimize dose to the adjacent nodal PTV is shown in Fig. 1.

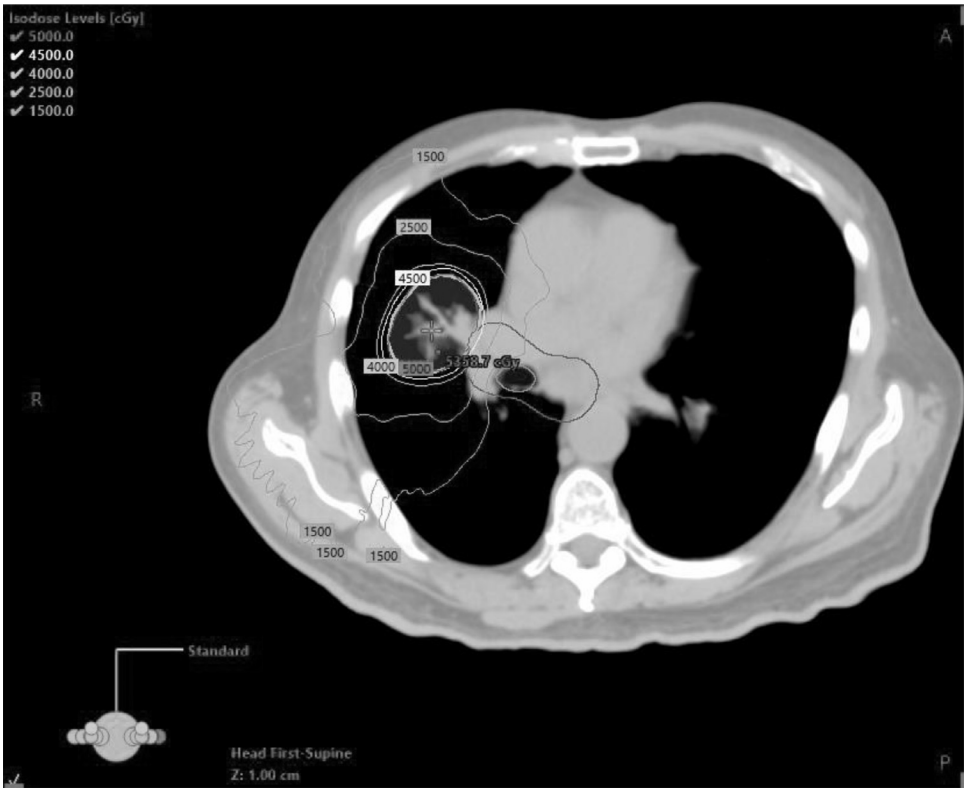

Figure 1 Representative plan of stereotactic body radiation therapy to the primary tumor. Fifty gray in 5 fractions was delivered to a central primary tumor (planning target volume primary in orange). Dose avoidance of planning target volume involved nodes (volume in red), proximal bronchial tree, and esophagus.

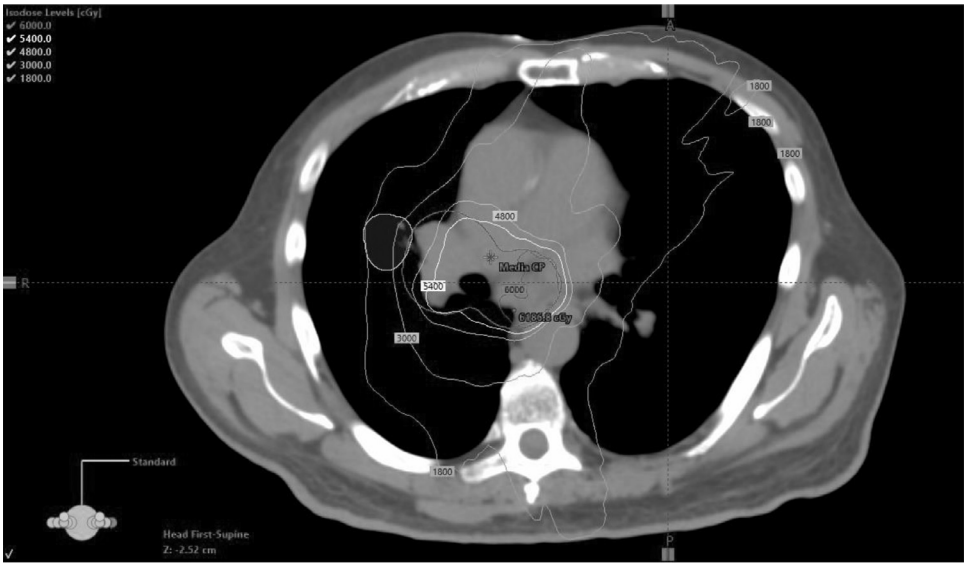

Figure 2 Representative plan of conventionally fractionated radiation to the involved planning target volume nodes (PTVn, in red). Sixty gray was delivered in 30 fractions with concurrent chemotherapy. Dose avoidance of planning target volume primary (pink) and intentional undercoverage of PTVn (red) (D95%: 84%).

Conventional radiation to the nodal disease planning

The conventionally fractionated radiation plans were delivered with 6 MV photons, and planning techniques included VMAT or dynamic multileaf collimator intensity modulated radiation therapy. VMAT arcs were typically coplanar, and most commonly 2 360° arcs were used. Less commonly, 2 180° or slightly greater than 180° arcs were used on the ipsilateral side. Dose rates up to 600 MU/min were used. The prescription dose per protocol was 60 Gy in 30 fractions. For the conventionally fractionated radiation plan to the involved nodal disease, optimization priorities were as follows: (1) to avoid intermediate dose overlap with the primary tumor PTV (PTVp), (2) sparing of central normal structures, especially those in which overlap of dose would occur, and (3) to attempt to achieve target volume coverage. For plans in which significant dose overlap was expected between the SBRT and conventional plans, the SBRT dose was used as a "base dose" when optimizing the conventional radiation plan. This could consist of a partial base dose of as low as 25% to as high as 100% of the SBRT dose delivered when optimizing target coverage on the conventional radiation plan. This technique would often lead to "under coverage" of the IGTVn, ICTVn, and PTVn than would typically be accepted on an individual plan to the nodal volumes. A plan summation would then be created, and the overall coverage of the IGTVn, ICTVn, and PTVn would be assessed so that D95% was at least 100% for the PTVn. Examples of individual nodal irradiation and SBRT and nodal irradiation summation plans are given in Figs. 2 and 3. Ideal plan summation contained the following priorities: (1) coverage of the PTVp to the intended SBRT dose per coverage requirements in Table 3, (2) overall coverage of the IGTVn, ICTVn, and PTVn to the coverage requirements in Table 3, (3) maximal optimization to limit dose overlap between the 2 plans, especially in central structures such as the proximal airways, esophagus, and heart, and (4) to meet overall normal structure constraints for SBRT and plan sum as outlined in Tables 2 and 4.

Quality assurance

Patient-specific quality assurance was performed for each plan with either a cylindrical or planar diode array (Sun Nuclear ArcCheck or MapCheck). When using the cylindrical phantom, patient plans were delivered using the planned gantry angles but with the treatment couch always at 0°, and the composite dose distribution was analyzed. The planar array was placed on the couch, all beams were delivered at a gantry angle of 0, and individual beams were analyzed. For SBRT plans to the primary tumor, quality assurance tolerance was 95% of points passing with a gamma criterion of 2% and 2 mm and a dose threshold of 10%. For the intensity modulated radiation therapy plans, tolerance was 95% of points passing with a gamma criterion of 3% and 2 mm and a dose threshold of 10%. Gamma analysis was performed in absolute dose mode.

Treatment

Patients were treated on various machines including those by Elekta (Stockholm, Sweden) and Varian (Palo

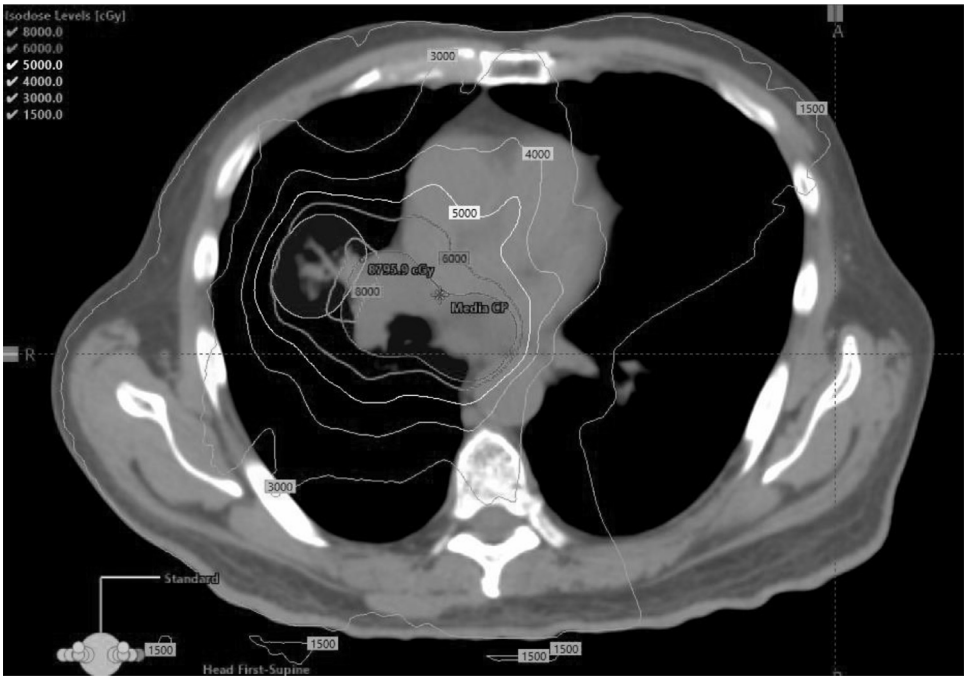

Figure 3 Representative plan summation of dose for stereotactic body radiation therapy to the primary tumor and involved nodal radiation (stereotactic body radiation therapy 50 Gy/5 fractions, involved nodal radiation 60 Gy/30 fractions). Dmax 88 Gy with high dose volume (80 Gy) not overlapping with central structures.

Alto, CA). Patients were set-up daily per the previous description, including the use of respiratory management if necessary. Daily image guidance was required with cone beam CT using volumetric match. For SBRT to the primary tumor, physician oversight during treatment was required to review the primary tumor match and treatment. For conventional radiation, cone beam CT and match were performed typically by the treating therapist with anatomic references used such as the major airways and visible IGTVn as would be typical for treatment to the lung with daily image guidance. Continuous surface guidance was allowed and used in most patients depending on availability.

Table 4 Normal structure constraints for dose summation of stereotactic body radiation therapy to the primary tumor and conventionally fractionated radiation to the nodal disease

Name of structure	Dosimetric parameter	Per protocol
Lungs: IGTV	V20 Gy	<37%
	Mean (Gy)	≤20
Spinal canal	D0.03cc (Gy)	≤50
Heart	V50%	≤40
Esophagus	Mean (Gy)	<34

Abbreviation: IGTV = Internal gross target volume.

Statistics

Dosimetric volume and planning characteristics were collected on all 60 subjects. These characteristics were summarized with descriptive statistics for continuous variables or with frequencies and proportions for categorical variables. Wilcoxon rank sum tests were used for evaluating continuous dosimetric parameters between those with and without adverse events of interest. Logistic regression was used to evaluate the effect of dichotomized dosimetric parameters on adverse event incidence.

Results

Dose and planning characteristics

Dose received on study for all 60 patients enrolled is summarized in Table 5. All patients except for 1 received 60 Gy in 30 fractions to the involved nodes. One patient, who was planned to 60 Gy in 30 fractions, had his treatment course stopped after 56 Gy in 28 fractions because of grade 3 esophagitis, which is detailed later in the manuscript. Planning techniques for both SBRT to the primary tumor and conventional radiation delivered to the involved lymph nodes are also summarized in Table 5.

Dosimetric coverage characteristics

Patient and tumor characteristics will be detailed in a subsequent efficacy outcomes manuscript, but dosimetric

Table 5 Dose and planning techniques used for SBRT to the primary tumor and conventionally fractionated radiation to the nodal disease

	N = 60	
SBRT to the primary	**No.**	**%**
Planning method		
DCA	1	1.7%
VMAT	59	98.3%
Total dose (Gy)/fractions		
50 Gy/4 fx	21	35.0%
50 Gy/5 fx	11	18.3%
54 Gy/3 fx	28	46.7%
Involved nodal radiation		
Planning method		
DMLC IMRT	3	5.0%
VMAT	57	95.0%
Total dose (Gy)/fractions		
56 Gy/28 fx	1	1.7%
60 Gy/30 fx	59	98.3%

Abbreviations: DCA = dynamic conformal arcs; DMLC = dynamic multileaf collimator; fx = fraction; IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy; VMAT = volumetric modulated arc therapy.

Table 6 Target volume and coverage ranges for both primary tumor stereotactic body radiation therapy and involved nodal radiation

	Median	Range
Age, y	71	52-82
IGTVp (cc)	11.2	0.3-121.5
IGTVn coverage D99%, (nodal plan) (% prescription dose)	100	18.5-100
IGTVn coverage D99%, (plan sum) (% prescription dose)	100	-
PTVp (cc)	31.3	3.4-205.4
PTVp coverage (SBRT plan) D95%, (%)	100	98-100
PTVn (cc)	122.9	8.6-467.8
PTVn coverage (nodal plan) D95%, (%)	100	32.9-100
PTVn coverage (nodal plan) D99%, (%)	96.6	11.5-100
PTVn coverage (plan sum) D95%, (%)	100	99-100
PTV combined, volume (cc)	162.7	42.0-508.6
ICTVn coverage (nodal plan) D99%, (%)	100	17.3-100
ICTVn coverage (plan sum) D99%, (%)	100	-

Abbreviations: ICTVn = internal clinical target volume nodal; IGTVn = internal gross target volume nodal; IGTVp = internal gross target volume primary; PTV = planning target volume; PTVn = PTV nodes; PTVp = primary tumor PTV.

Table 7 Doses to select normal tissues from the combination dose of stereotactic body radiation therapy to the primary tumor and involved nodal radiation

Plan sum overall max D0.03cc (Gy)	**Median 76.8**	**Range 63-106**
Lungs: IGTV combined		
V20 (%)	22.0	7.1-35
V10 (%)	42.4	22-71
V5 (%)	54	34-89
Mean dose (Gy)	12.8	5.4-22.0
Esophagus		
Mean dose (Gy)	17.0	3.3-33.0
Max dose (D0.03cc) (Gy)	63.5	26.5-78.0
V60 (%)	4.4	0-25
D1cc (Gy)	61	24-75
Heart		
D0.03cc (Gy)	64	2.0-77.5
D50% (Gy)	1.7	0.4-20.0
D35% (Gy)	2.8	0.6-27.0
Other OARs of interest		
Proximal broch tree max dose D0.03cc (Gy)	66	62.5-88
Great vessel max dose D0.03cc (Gy)	68	32-85
Brachial plexus max D0.03cc (Gy)	12.5	2-65
Chest wall D0.03cc (Gy)	59	26-75
Chest wall D5cc (Gy)	48.8	18-65.5
Spinal cord D0.03cc (Gy)	29	2.7-48

Abbreviations: IGTV = internal gross target volume; OAR = organ at risk.

target volumes and coverages are summarized in Table 6. Of note, the PTVn coverage D95% on the conventionally fractionated plan ranged from 32.9 to 100, but PTVn on the plan sum ranged from 99 to 100.

Normal tissue dosimetric results

Table 7 details dose to select normal tissue on the plan sum dose. Reasonable max point doses to normal tissues of interest were able to be achieved with the planning methods as outlined.

Toxicity

Toxicity specific to thoracic radiation (either SBRT to the primary or conventional radiation to the involved lymph nodes) is reported in this manuscript with other toxicities, including those from systemic therapies, to be detailed in a subsequent efficacy outcomes manuscript. At the time of this report the median follow-up was 23.23 months. This

Table 8 Dosimetric parameters evaluated for correlation with grade 2 or higher pneumonitis (21.7% incidence)

	Event (n = 13) Median (range)	No event (n = 47) Median (range)	*P* value Wilcoxon test	Significance threshold
V20 Gy (%)	27 (9-35)	22 (7.1-35)	.156	
V10 Gy (%)	46 (25-67)	41 (22-71)	.156	>45%
V5 Gy (%)	58 (40.5-82)	52 (34-89)	.074	>70%
Mean lung dose (Gy)	14 (7-18.6)	12 (5.4-22)	.118	
Proximal broch tree max dose (Gy)	64.5 (62.5-74)	67.5 (63-88)	.094	

Table 9 Dosimetric parameters evaluated for correlation with grade 2 or higher esophagitis (45% incidence)

	Event (n = 27) Median (range)	No event (n = 33) Median (range)	*P* value Wilcoxon test	Significance threshold
Esophagus mean dose (Gy)	20.4 (8-33)	15.5 (3.3-27)	.011	>20 Gy
Esophagus max dose (D0.03cc) (Gy)	64 (38-75)	62 (26.5-78)	.173	
Esophagus V60 (%)	8.7 (0-25)	0.8 (0-22.4)	.007	>7%
Esophagus D1cc (Gy)	63 (33-70)	56.5 (24-75)	.030	>55 Gy

report includes both acute and late toxicity as patients were followed for up to 5 years in this study. Of particular interest to this report were pulmonary, esophageal, and cardiac toxicities. Only 1 patient (1.7%) had chest wall toxicity, grade 2. For pulmonary toxicity, grade 2 or higher pneumonitis was seen in 21.7% of patients, with grade 3 pneumonitis seen in only 3 patients (5.0%). Higher V5 Gy was associated with increased risk of grade 2 or higher pneumonitis (Table 8), with associations greatest with values of 70% or higher. V10 Gy values of 45% or higher also correlated with increased risk of grade 2 or higher pneumonitis. When including any grade 2 or higher pulmonary toxicity, higher V10 Gy was associated with higher risk, especially with values of ≥50. Only 1 patient (1.7%) had grade 3 esophagitis. His esophageal doses were moderate, with a max cumulative point dose of 62 Gy, V60 of 9.2%, D1cc of 62 Gy, and mean dose of 20.0 Gy on the plan summation. Grade 2 or higher esophagitis occurred in 45.0% of patients on study. Esophagus mean dose, V60 Gy, and D1cc correlated with higher rates of esophagitis (Table 9). For esophagus mean dose, values >20 Gy were associated with higher risk of grade 2 esophagitis, along with V60 Gy values >7% and D1cc values >55 Gy. Grade 3 or higher cardiotoxicity was only seen in 3 patients (5%; heart failure, n = 2; chest pain, n = 1), with none of them determined to be possibly, probably, or definitely related to radiation. Given the low rate of cardiac events seen in the study, none of the heart dosimetric outcomes correlated with increased risk.

Discussion

SBRT has now become standard-of-care therapy in stage I medically inoperable NSCLC and has shown improved results over conventionally fractionated radiation.[4,5,11,12] Utilization of SBRT in locally advanced NSCLC has been previously attempted, mainly as a boost method as part of conventionally fractionated radiation.[13-16] The results of these studies have shown increased toxicity, especially for larger, more central disease. Our institution completed a phase 2 study evaluating full-dose SBRT to the primary tumor followed by chemoradiation with fractionated radiation to the involved lymph nodes with promising early efficacy and toxicity results. These results have led to the evaluation of SBRT in the treatment of locally advanced NSCLC in a newly activated phase 3 trial, NRG Oncology LU-008.

On the phase 2 study, toxicity was minimized by preferentially sparing normal structures with unique planning approaches and prioritization of specific normal tissues over target coverage. This manuscript describes those priorities and techniques to allow such approaches to be replicated in other community and academic practices. Results of the dosimetric analyses show that overall, plan summation of the SBRT and conventionally fractionated plans resulted in low maximum doses to specific normal tissues such as the esophagus, proximal bronchial tree, heart, great vessels, and spinal cord. Plan summation of the SBRT dose to the primary tumor and the conventionally fractionated dose to the nodal target volume also adequately covered primary tumor and lymph node targets, even when those targets may not have been covered to traditional doses in the respective individual plans. Toxicity results show this treatment to be well tolerated, with acceptable or even improved rates of pneumonitis and esophagitis compared with other conventional studies. Typical dosimetric thresholds often used in evaluation of plan quality for LA NSCLC were evaluated. Based on the

threshold values for toxicity seen in this study, formal parameters for lung and esophageal dose have been developed for NRG Oncology LU-008.

Conclusion

SBRT to the primary tumor followed by chemoradiation with fractionated radiation to the involved lymph nodes can be safely administered for locally advanced NSCLC. This manuscript serves both as a report of dosimetric outcomes for a completed phase 2 study as well as a guide for implementation of planning techniques at centers who elect to open the phase 3 study evaluating this regimen, NRG LU-008.

Disclosures

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