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Stereotactic body radiation therapy for isolated hilar and mediastinal non-small cell lung cancers☆

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ABSTRACT

Objectives: The seminal phase II trial for pulmonary stereotactic body radiation therapy (SBRT) suggested that SBRT to central lesions resulted in unacceptable toxicity. Alternative dose-fractionation schemes have been proposed which may improve safety without compromise of efficacy. We report our institutional outcomes of SBRT for hilar/mediastinal non-small cell lung cancer (NSCLC).

Materials and methods: A retrospective review was conducted of patients with NSCLC in a hilar or mediastinal nodal station which was treated with SBRT. Patients presented with a lesion involving the hilum or mediastinum from primary or oligorecurrent NSCLC. Kaplan-Meier with log-rank testing and Cox analysis were utilized for outcomes analysis.

Results: From 2008–2015, 40 patients with median age of 70 were treated with SBRT for primary/oligorecurrent hilar/mediastinal NSCLC with median follow-up of 16.4 months. 85% presented with oligorecurrent disease at a median of 22.4 months following definitive therapy. The aortico-pulmonary window was the target in 40%, the hilum in 25%, lower paratracheal in 20%, subcarinal in 10%, and prevascular in 5%. The median dose was 48 Gy in 4 fractions (range: 35–48 Gy in 4–5 fractions).

Median overall (OS) and progression-free (PFS) survivals were 22.7 and 13.1 months, respectively. Two-year local control was 87.7% and not significantly different between hilar and mediastinal targets. Median PFS was significantly improved in patients with hilar vs mediastinal nodal targets: 33.3 vs 8.4 months, respectively ($p = 0.031$). OS was not statistically different between hilar and mediastinal targets ($p = 0.359$). On multivariable analysis, hilar vs mediastinal target predicted for PFS (HR 3.045 95%CI [1.044–8.833], $p = 0.042$), as did shorter time to presentation in patients with oligorecurrence (HR 0.983 [95%CI 0.967–1.000], $p = 0.049$). Acute grade 3+ morbidity was seen in 3 patients (hemoptysis, pericardial/pleural effusion, heart failure) and late grade 3+ morbidity (hemoptysis) in 1 patient.

Conclusion: Hilar/mediastinal SBRT appears to be a safe technique for the local control of isolated nodal disease with limited toxicity from the fractionation schemes utilized.

1. Introduction

Following early phase II results for pulmonary stereotactic body radiation therapy (SBRT), a "no fly zone" was established within 2 cm of the trachea and proximal bronchial tree because of > 50% grade 3–5 toxicity [1]. Patients with tumors within this region were subsequently excluded from the seminal RTOG trial on pulmonary SBRT for medically inoperable non-small cell lung cancer (NSCLC) patients using 54 Gy in 3 fractions [2]. A recent survey of German/Swiss radiation oncologists demonstrated a high level of physician comfort in treating lesions up to 4 cm with a minimal distance of 2 cm from the mainstem bronchi, but gave mixed responses when lesions lay within that minimal distance, indicating some non-adherence to the "no fly zone" rule [3]. To lend credence to the safety and efficacy of doing so, several institutions have published their experiences on alternative fractionation schedules in the treatment of lesions which lie within the "no fly zone [4–9]."

Since tumors that arose within the "no fly zone" had been previously excluded from prospective study, the RTOG launched protocol 0813, a phase I/II dose-escalation study to determine the maximum tolerated dose in this region. Results were recently reported that the highest per-protocol dose-level was achieved (12 Gy × 5 fractions)

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with 7.2% grade 3+ toxicity, though conclusions regarding the optimal fractionation schedule were left open until the phase II portion of the trial is complete [10].

The "no fly zone" encompasses a number of different critical structures and only two single-institution reports have explicitly detailed the location of treated lesions as being contained within the mediastinum [7,9]. We therefore sought to describe our institutional experience in treating primary and oligorecurrent NSCLC involving the hilar and mediastinal lymph nodes with a focus on the targeted stations with regards to control, patterns of failure, and toxicity. Furthermore, we expect use of SBRT to treat oligo-nodal disease can be performed with a similar safety and toxicity profile as seen with similar protracted SBRT regimens for centrally-located parenchymal lesions.

2. Methods

A retrospective institutional review board-approved study was conducted using the stereotactic database collected within the xxxx from 2008 to 2015. All patients presenting with a primary non-small cell lung cancer involving the hilar or mediastinal nodes (TxN+) or isolated oligorecurrence to these sites following definitive therapy for NSCLC were identified and patients treated with SABR were evaluated.

CT simulation was performed with each patient raising their arms above their heads. Patients were immobilized with a custom BodyFix™ immobilization device. A 4DCT was performed and Varian Real-Time Position Management System (Varian Medical Systems, Palo Alto, CA) was used to account for respiratory cycle motion seen on imaging. Contouring was performed on CT phase 50% (maximum expiration) and motion was assessed as to the need for a gating window to limit to 5 mm or less in any direction. All patients with tumor motion > 0.5 cm underwent respiratory gating. Accuray MulitPLAN™ (Accuray, Inc, Sunnyvale, CA) or Varian Eclipse™ (Varian Medical Systems, Palo Alto, CA) were used to transfer images to treatment planning workstations. The esophagus, heart, brachial plexus, normal lung, and spinal cord were all critical structures included the plans.

The target consisted of a GTV which was the gross nodal disease visualized on CT planning. The PTV consisted of a 5 mm expansion with editing out of normal structures. Dose regimens were selected based on NCCN SBRT critical organ dosimetry limits [11]. The goal was for the PTV to receive 95% of the prescription dose while respecting critical organ tolerances. If critical organ restrictions were not met then PTV coverage was lowered.

Overall survival (OS) and progression-free survival (PFS) were calculated from the first day of SBRT. Comparisons between cohorts (hilar and mediastinal nodes) were made with bivariate regression analysis. Survival curves were generated with Kaplan-Meier method and compared with log-rank test. Uni- and multivariate comparisons were performed with Cox regression analysis. Significance for inclusion in the multivariate model was set at $p < 0.10$ and $p < 0.05$ as a significant predictor of outcomes.

3. Results

From 2008–2015, 40 patients were identified who met our inclusion criteria. Patient and treatment characteristics are presented in Table 1. The majority of patients (85%) presented with oligorecurrent disease at a median of 22.4 months following definitive therapy, with a relatively homogeneous distribution of surgery and radiation as the means of initial local therapy. The most common SBRT dose-fractionation was 48 Gy in 4 fractions, although other fractionation schemes of 45, 40, and 35 Gy in 5 fractions were all utilized to respect normal tissue tolerances as necessary (Table 2). Ten patients were treated to hilar targets and 30 patients were treated to mediastinal targets. The most commonly targeted nodal stations were: aortico-pulmonary window (40%), hilum (25%), lower paratracheal (20%), subcarinal (10%), and prevascular (5%). Patients treated to hilar nodes tended to have better performance status ($p = 0.025$) and were more likely to have primary disease as opposed to oligorecurrent disease ($p = 0.022$), and there was a trend toward larger target volumes with hilar versus mediastinal targets ($p = 0.075$) but no other differences in baseline characteristics were noted.

Table 1
Patient, tumor, and treatment characteristics.

	Value (%)			
	All Patients	Hilar	Mediastinal	p
Sex				1.000
Male	16 (40%)	4 (40%)	12 (40%)	
Female	24 (60%)	6 (60%	18 (60%)	
Median Age (Range)	70 (47–95)	71 (56–95)	70 (47–88)	0.695
Median KPS (Range)	80 (70–100)	90 (70–90)	80 (70–100)	**0.025**
Tumor Type				**0.022**
Primary	6 (15%)	4 (40%)	2 (7%)	
Oligorecurrent	34 (85%)	6 (60%)	28 (93%)	
Histology				0.632
Adenocarcinoma	18 (45%)	5 (50%)	13 (43%)	
Squamous Cell Carcinoma	14 (35%)	5 (50%)	9 (30%)	
NSCLC not specified	8 (20%)	0 (0%)	8 (27%)	
Prior Surgery				0.128
Yes	13 (32%)	1 (10%)	12 (40%)	
No	27 (68%)	9 (90%)	18 (60%)	
Prior Radiation				0.111
Yes	20 (50%)	3 (30%)	17 (57%)	
No	20 (50%)	7 (70%)	13 (43%)	
Prior Chemotherapy				0.439
Yes	34 (87%)	8 (80%)	26 (90%)	
No	5 (13%)	2 (20%)	3 (10%)	
Median SUV (range)	6.70 (3.60–16.70)	6.70 (4.10–13.40)	6.90 (3.60–16.70)	0.897
Median GTV (cc) (range)	7.25 (0.70–88.30)	11.25 (1.70–88.30)	7.25 (0.70–55.90)	0.074
SBRT Dose – median	**48 Gy/4fx**	**48 Gy/4fx**	**48 Gy/4fx**	0.934
35 Gy/5fx	**1**	**0**	**1**	
40gy/5fx	**6**	**0**	**6**	
45gy/5fx	**10**	**3**	**7**	
48gy/4fx	**23**	**7**	**16**	
Post-sbrt CHEMOTHERAPY	22 (55%)	7 (70%)	15 (50%)	0.321

The differences in dose fractionation were not analyzed indifidually, but rather as differences in median dose between hilar and mediastinal targets, with p = 0.934. Dashes can be placed in the p column for those 4 subvalues.

4. Disease outcomes

Median follow-up was 16.4 months (range: 0.7–84.5 months) for all patients and 42.1 months (range: 10.2–84.5 months) for patients still living. Overall, 3 patients (7.5%) experienced local failure and 9 (22.5%) had regional failure. Isolated nodal mediastinal failures were seen in six patients (15%), all of which occurred in patients with oligorecurrent disease and a mediastinal station target. Fourteen patients (35%) experienced distant failure.

At two years, local control was 87.7%. All local failures occurred in male patients ($p = 0.045$), but no other factors, including SBRT dose and tumor size predicted for local control. Regional control was 64.3% at two years. Excluding patients who failed simultaneously outside of the mediastinum, the 2-year mediastinal control was 83.9% with all mediastinal failures occurring in the first year. All isolated nodal failures occurred in patients with mediastinal targets and 2-year control rates were 100% and 77.9% for patients with hilar and mediastinal targets, respectively (Fig. 1A, $p = 0.117$). All isolated mediastinal failures occurred in patients with oligorecurrent disease as well ($p = 0.261$) and all such failures occurred within one year of treatment. Distant control at one and two years was 66.1% and 48.1%, respectively. There was a trend toward improved distant control after