Changes in Pulmonary Function Following Image-Guided Stereotactic Lung Radiotherapy

Neither Lower Baseline Nor Post-SBRT Pulmonary Function Are Associated with Worse Overall Survival

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Purpose: To determine changes in pulmonary function brought about by lung stereotactic body radiation therapy (SBRT).

Methods: One hundred and twenty-seven patients were treated with lung SBRT using 48 to 60Gy in four to five fractions on a prospective trial. We obtained pulmonary function tests (PFTs) at baseline, 6 weeks, 3 months, 6 months, 9 months, 12 months, and 24 months after SBRT. Group mean PFT parameter values are reported.

Results: At baseline forced expiratory volume in 1 second (FEV1) was 1.5 l (67% predicted, range: 0.4–3.4 l), corrected diffusing capacity for carbon monoxide was 12.2 ml/min/mmHg (50.8% predicted, range: 3.3–27.2 ml/min/mmHg), and total lung capacity was 5.7 l (102.4% predicted, range: 3.1–9.1 l). At 12 months, there was decline in FEV1 (−4.1%; $p = 0.01$), corrected diffusing capacity for carbon monoxide (−5.2%; $p = 0.027$), forced vital capacity (−5.7%; $p = 0.004$), and total lung capacity (−3.6%; $p = 0.039$). Declines in FEV1 (−7.6%; $p = 0.001$) and forced vital capacity (−8.9%; $p = 0.001$) persisted at 24 months. Rates of pneumonitis were 3.1% and 0.8% for grades 2 and 3, respectively. There were no grade 3 PFT toxicities at 12 months. Lower PFTs at baseline and 1 year after SBRT did not predict for worse overall survival.

Conclusions: As the largest cohort of patients with prospective follow-up PFT evaluation after lung SBRT, this supports the safety of SBRT in this population of predominantly medically inoperable patients. While statistically significant, nearly all declines in PFTs would be rated as a grade 1 on the Radiation Therapy Oncology Group scale, demonstrating safety. PFT declines were not associated with worse overall survival.

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Although surgical resection with a lobectomy remains the standard of care for early stage non–small-cell lung cancer (NSCLC), treatment of these lesions with stereotactic body radiotherapy (SBRT) is an increasingly attractive alternative for patients who are not surgical candidates.

Multiple studies have examined pulmonary function after lobectomy.[1–4] In these prior studies, reductions have been observed in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), diffusing capacity of carbon monoxide (DLCO), and maximum oxygen consumption (VO2max).

Harada et al.[5] demonstrated that smaller reductions in FEV1 and FVC were possible with a segmentectomy compared with a lobectomy. However, the LCSG randomized trial comparing limited resection with either a segmentectomy or wedge resection with lobectomy revealed improved local control rates with lobectomy.[6]

Choi and Kanarek[7] prospectively evaluated changes in pulmonary function in lung cancer patients undergoing conventional fractionated radiotherapy (RT) with or without chemotherapy. These authors reported significant declines in DLCO (27% reduction), FEV1 (19%–20% reduction), total lung capacity (TLC; 13% reduction) up to 12 months after RT. However, this was only significant in patients with a baseline percent predicted FEV1 greater than or equal to 50%.

We have previously reported on our institutional experience with SBRT for limited stage NSCLC and have found excellent local control rates at 2.5 years.[8]

Here, we present the changes observed in pulmonary function tests (PFTs) in patients treated according to our single institution phase II study of lung SBRT for early stage NSCLC.

PATIENTS AND METHODS

Patient Eligibility

A total of 127 patients with AJCC 7 clinical stage I (T1–T2 N0 M0) peripheral NSCLC or a solitary lung

metastasis from another primary tumor were treated with image-guided stereotactic lung RT using daily online volumetric guidance via cone-beam computed tomography (CBCT; Elekta Synergy or Axesse) as part of a single institution Phase II clinical trial between November 2005 and July 2012. This research was conducted with institutional review board approval. Participants were either deemed inoperable secondary to comorbid medical illness or poor PFTs or they had refused surgery. All tumors were ≤5 cm in size and judged to be technically resectable by an experienced thoracic surgeon.

All patients underwent a comprehensive staging work up including a complete history and physical exam, CT scan of the chest and upper abdomen, ^{18}FDG-positron emission tomography (PET) scan, magnetic resonance imaging brain, fine needle aspiration or core biopsy of the lesion, routine laboratory studies, and baseline PFTs. If equivocal nodal disease was seen on PET or CT scans, a mediastinoscopy or bronchoscopy was performed.

Pulmonary Function Tests

PFTs were obtained at baseline (within 10 weeks of SBRT) and subsequently at 6 weeks, 3 months, 6 months, 9 months, 12 months, and 24 months after SBRT. Studies evaluated FEV1, FVC, DLCO, TLC, diffusing capacity for carbon monoxide divided by alveolar volume (DLCO/VA), and arterial blood gases. DLCO values were corrected according to hemoglobin level. PFTs were acquired and interpreted according to joint American Thoracic Society and European Respiratory Society guidelines.[9–12] Prebronchodilator values are reported and analyzed, for both baseline and follow-up time points.

Radiation Simulation/Planning

All patients underwent a virtual radiation simulation with immobilization in a stereotactic body frame (Elekta Oncology, Norcross, GA), Body Fix (Elekta Oncology), or alpha-cradle (KGF Enterprises, Chesterfield, MI). Early in study accrual, respiratory tumor motion was screened using fluoroscopy. If tumor motion was not easily visualized or greater than 5 mm, a four-dimensional-CT (4D-CT; Philips Medical Systems, Milipitas, CA) was performed. After the first several patients were enrolled, a 4D-CT and a free-breathing CT were obtained for all subsequent patients.

These data were transferred to the treatment planning workstation (Philips Pinnacle v7.4f, Milipitas, CA), and subsequently registered and fused with a treatment planning PET scan, typically obtained with the patient in the same immobilization device. The tumor was outlined on sequential axial CT slices to create the gross tumor volume (GTV). Adjacent normal structures were also contoured. GTV was defined as the tumor visualized on CT lung windows unionized with the GTV as defined by PET, and GTV as defined in 10 phases of the respiratory cycle for all cases where a 4D-CT was available, rendering a final $GTV_{internal\ target\ volume}$ (GTV CT + GTV PET + GTV phase1 + GTV phase2 + GTV phase3…GTV phase10 = GTV ITV). As described in a prior publication,[13] the clinical target volume consisted of the GTV ITV with a 4 mm expansion (CTV = GTV ITV + 4 mm). The planning target volume (PTV) consisted of a minimum 5 mm expansion of the CTV in three dimensions, but depended on the extent of tumor motion during respiration for each patient.

A stereotactic RT plan was designed using a combination of six to nine coplanar and noncoplanar beam angles and a limited number of couch angles. A function of the Pinnacle software originally designed for intensity-modulated radiotherapy was adapted for use as an engine to inversely optimize the beam aperture and weighting. The direct machine parameter optimization algorithm was constrained to allow only a single segment per beam. Dose volume objectives were used to develop an inversely optimized treatment plan. Only the beam weight and aperture were optimized; intensity-modulated radiotherapy was therefore not routinely employed although was used in select cases to meet normal tissue dose volume constraints, and volumetrically-modulated arc therapy (VMAT) was used in more recent years.

A dose of 48 Gy in four fractions (12 Gy × 4) or 60 Gy in five fractions (12 Gy × 5) was prescribed to the PTV edge (60%–90% isodose line, but typically the 80% isodose line) for T1 and T2 or metastatic tumors, respectively. Lung dose volume constraints used during planning optimization aimed to achieve the following goals for the lungs-GTV volume: (1) V20 ≤ 10% (11%–15% considered minor violation), (2) V10 or V12.5 ≤ 15%, and (3) mean lung dose less than 10 Gy. Only the V20 and mean lung dose constraints were required to be met for study entry, however. All treatments were delivered using daily online CBCT-based volumetric IGRT with soft tissue target registration. Decadron 4 mg orally was given 15 to 30 minutes before each fraction. Treatment was delivered with a minimum of 40 hours and a maximum of 4 days between fractions.

Both the Radiation Therapy Oncology Group (RTOG) PFT toxicity scale (grade 1: 10%–25% decline; grade 2: >25%–50% decline; grade 3: >50%–75% decline; grade 4: >75% decline; grade 5: death) and the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) were used for grading adverse events.[14,15]

Patient characteristics, disease information, and lung dose volume planning parameters were included in the descriptive analysis. The relative changes of pulmonary function were calculated from baseline and tested by paired *t* test. Correlation was tested for tumor and treatment characteristics. Overall survival (OS) was calculated from the last date of SBRT to the date of last follow-up or death. The likelihood of events was calculated by the Kaplan–Meier method. The statistical significance between actuarial rates was calculated with log-rank test. Results were considered statistically significant if p value less than 0.05. SPSS version 20 (IBM, Armonk, NY) was used for analysis.

RESULTS

A total of 127 patients were treated with lung SBRT between November 2005 and July 2012. The median follow-up was 25 months (range: 1–85 months). The 1- and 3-year OS rates for all patients were 87% and 62%, respectively. The baseline patient characteristics are outlined in Table 1.

