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CLINICAL INVESTIGATION **Thoracic Cancer**

PREDICTION OF CHEST WALL TOXICITY FROM LUNG STEREOTACTIC BODY RADIOTHERAPY (SBRT)

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Purpose: To determine patient, tumor, and treatment factors related to the development of late chest wall toxicity after lung stereotactic body radiotherapy (SBRT).

Methods and Materials: We reviewed a registry of 134 patients treated with lung SBRT to 60 Gy in 3 fractions who had greater than 1 year of clinical follow-up and no history of multiple treatments to the same lobe ($n = 48$). Patients were treated as per Radiation Therapy Oncology Group Protocol 0236 without specific chest wall avoidance criteria. The chest wall was retrospectively contoured. Thirty-two lesions measured less than 3 cm, and sixteen measured 3 to 5 cm. The median planning target volume was 29 cm^3.

Results: With a median follow-up of 18.8 months, 10 patients had late symptomatic chest wall toxicity (4 Grade 1 and 6 Grade 2) at a median of 8.8 months after SBRT. No patient characteristics (age, diabetes, hypertension, peripheral vascular disease, or body mass index) were predictive for toxicity, whereas there was a trend for continued smoking ($p = 0.066$; odds ratio [OR], 4.4). Greatest single tumor dimension ($p = 0.047$; OR, 2.63) and planning target volume ($p = 0.040$; OR, 1.04) were correlated with toxicity, whereas distance from tumor edge to chest wall and gross tumor volume did not reach statistical significance. Volumes of chest wall receiving 30 Gy (V30) through 70 Gy (V70) were all highly significant, although this correlation weakened for V65 and V70 and maximum chest wall point dose only trended to significance ($p = 0.06$). On multivariate analysis, tumor volume was no longer correlated with toxicity and only V30 through V60 remained statistically significant.

Conclusions: Tumor size and chest wall dosimetry are correlated to late chest wall toxicity. Only chest wall V30 through V60 remained significant on multivariate analysis. Restricting V30 to 30 cm^3 or less and V60 to 3 cm^3 or less should result in a 10% to 15% risk of late chest wall toxicity or lower. © 2012 Elsevier Inc.

Stereotactic body radiotherapy, SBRT, Chest wall toxicity, Lung cancer, Stage I.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) provides excellent local control for patients with medically inoperable Stage I non–small-cell lung cancer, as well as select patients with pulmonary oligometastases (1–15). In general, treatment is very well tolerated with a low incidence of acute and late toxicity. Late chest wall toxicity has been described in the literature, including skin changes (erythema, ulceration and fibrosis) (16), chest wall pain (focal or neuropathic), and rib fracture (symptomatic and asymptomatic) (1, 4, 5, 7, 8, 10–12, 17–20).

Chest wall toxicity is typically mild or moderate and treated effectively by oral anti-inflammatory medication, gabapentin, or narcotics. Skin changes may be seen 3 to 6 weeks after treatment (16), whereas chest wall pain and rib fracture typically occur substantially later, with a median time to onset of greater than 6 months after SBRT (17–21). At present, few data exist to guide informed consent and treatment planning with respect to symptomatic chest wall toxicity after SBRT. We have previously noted a greater incidence of chest wall toxicity in peripheral lesions treated to 60 Gy in 3 fractions as opposed to 50 Gy in 5 fractions (18% vs. 4%) (19). Meanwhile, in two separate dose–volume analyses, a Swedish study found the strongest association between individual rib dose–volume histogram parameters and fracture risk in the small-volume/high-dose region (18) whereas a second study found strong correlations with both the volume of chest wall receiving 30 Gy (V30) and small-volume/high-dose regions, such as V60 (17).

These studies differ in terms of the selection criteria and length of follow-up of patients, SBRT fractionation used, and dosimetric volume of interest studied. We present an analysis of patient, tumor, and treatment factors and their correlation with late chest wall toxicity in patients treated

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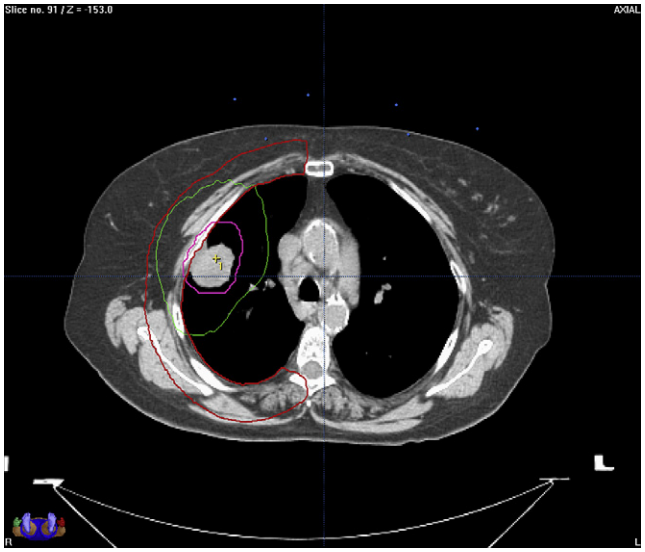

Fig. 1. Chest wall contour.

with thoracic SBRT. All patients were treated with a uniform treatment regimen of 60 Gy in 3 fractions and have sufficient follow-up to detect most chest wall events. Our aim is to both help predict the risk of toxicity for individual patients and assist with establishing treatment planning parameters to minimize this risk.

METHODS AND MATERIALS

Patient selection and evaluation

This is a retrospective review of an institutional review board–approved registry of 134 patients treated between February 2005 and February 2008 with SBRT for isolated lung lesions measuring less than 5 cm. We limited our analysis to patients who either had chest wall toxicity before 1 year or had no toxicity with clinical follow-up of at least 1 year (n = 117) and were treated to 60 Gy in 3 fractions (n = 51). Patients with previous radiation or multiple SBRT treatments to the same lobe were then excluded (n = 3), leaving a final population of 48 patients who were analyzed for this study (40 with primary non–small-cell lung cancer and 8 with oligometastatic lesions). Oligometastatic patients had only a single metastatic lesion in the lung with greater than 2 years from their primary diagnosis in all cases.

Patient factors analyzed included age, gender, smoking history, smoking status, body mass index (BMI), and the presence of diabetes, hypertension, or peripheral vascular disease at the time of consultation. Tumor factors included greatest tumor dimension on computed tomography (CT), gross tumor volume (GTV), closest distance from tumor periphery to chest wall on planning CT scan, and planning target volume (PTV). Treatment factors included chest wall dosimetry (absolute volume in cubic centimeters receiving 30 Gy through 70 Gy, in 5-Gy increments), maximum chest wall point dose, heterogeneity index (maximum point dose divided by prescription dose), and conformality index (prescription volume/PTV). Chest wall was contoured as the arc of all ipsilateral soft tissue outside of lung tissue from the edge of the sternum circumferentially to the edge of the vertebral body including the spinal nerve root exit site (Fig. 1). All mediastinal tissue was excluded. Although all the patients were originally planned without heterogeneity correction, for the purposes of this analysis, all plans were recalculated with heterogeneity corrections enabled to better approximate the true dose delivered.

Patients were followed up 6 to 8 weeks after SBRT, and then every 3 months thereafter, with CT imaging at each visit. Positron emission tomography scans were obtained when imaging or clinical findings suggested the possibility of recurrence. Chest wall toxicity was defined clinically according to a modified version of the Common Terminology Criteria for Adverse Events version 3.0 including all symptomatic skin ulceration, focal chest wall pain, and neuropathic pain: Grade 1, mild pain, no need for narcotics; Grade 2, moderate pain, narcotics indicated; Grade 3, severe pain/pain or treatment interferes with activities of daily living, long-acting or scheduled narcotics indicated; and Grade 4, disabling. Asymptomatic rib fractures were not scored. Patients whose toxicity level changed over time were scored at the time of greatest toxicity.

Treatment procedure

Patients were simulated supine in a vacuum bag restriction system (Bodyfix; Elekta, Stockholm, Sweden). An abdominal compression device was applied to reduce respiratory movement and adjusted under fluoroscopy. A planning axial CT scan with 3-mm slice thickness was taken during quiet breathing, full inspiration, and full expiration. Treatment plans were generated by BrainScan 5.31 planning software (BrainLAB, Feldkirchen, Germany) referenced to the free-breathing study. Patients were treated on the Novalis system (BrainLAB) by use of orthogonal films and the ExacTrac stereotactic body system (BrainLAB) for positioning. Target volume and critical structure definitions, as well as planning goals and restrictions, were strictly as per Radiation Therapy Oncology Group Protocol 0236 (22). No planning decisions were made based on proximity to chest wall, and no chest wall dosimetric constraints were used. Patients received 60 Gy in 3 fractions over a period of 8 to 14 days delivered via 6-MV photons by use of one to seven dynamic arcs.

Statistical analysis

The primary endpoint was development of clinical chest wall toxicity during the follow-up interval. Logistic regression analysis was used to correlate patient, tumor, and treatment factors to clinical chest wall toxicity in both univariate and multivariate models. Statistical analyses were performed with StatView 5.0 (SAS Institute, Cary, NC), and $p < 0.05$ was considered statistically significant. Finally, by use of the logistic regression models, probability curves for chest wall toxicity were created for the tumor and dosimetric parameters of interest. The probability of chest wall toxicity was based on the odds ratios:

$$\text{Probability of Chest Wall (CW) toxicity by Variable} = \frac{e[\text{coefficient of constant} + (\text{Natural Log (LN) Odds ratio} * \text{Variable})]}{1 + e[\text{coefficient of constant} + (\text{LN Odds ration} * \text{Variable})]}$$

RESULTS

Forty-eight lesions in forty-five patients met all inclusion criteria. Two patients had synchronous bilateral lesions, whereas one patient had a synchronous unilateral upper and lower lobe lesion. No patient with multiple lesions had toxicity. Patient characteristics are shown in Table 1. Thirty-two lesions measured less than 3 cm, whereas sixteen measured 3 to 5 cm. The overall median size was 2.15 cm,

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