Central versus Peripheral Tumor Location

Influence on Survival, Local Control, and Toxicity Following Stereotactic Body Radiotherapy for Primary Non–Small-Cell Lung Cancer

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Introduction: Stereotactic body radiotherapy (SBRT) has been increasingly utilized for medically inoperable early stage non–small-cell lung cancer. However, a lower biological equivalent dose (BED) is often used for central tumors given toxicity concerns, potentially leading to decreased local control (LC). We compared survival, LC, and toxicity outcomes for SBRT patients with centrally versus peripherally located tumors.

Methods: We included patients with primary cT1-2N0M0 non–small-cell lung cancer treated with SBRT at our institution from September 2007 to August 2013 with follow-up through August 2014. Central tumor location was defined as within 2 cm of the proximal bronchial tree, heart, great vessels, trachea, or other mediastinal structures. Kaplan–Meier analysis and multivariable Cox regression modeling were used for overall survival (OS) and LC, and the χ^2 test and multivariable logistic regression modeling were used for toxicity.

Results: We included 251 patients (111 central, 140 peripheral) with median follow-up of 31.2 months. Patients with central tumors were more likely to be older (mean 75.8 versus 73.5 years; $p = 0.04$), have larger tumors (mean 2.5 cm versus 1.9 cm; $p < 0.001$), and be treated with a lower BED (mean 120.2 Gy versus 143.5 Gy; $p < 0.001$). Multivariable analysis revealed that tumor location was not associated with worse OS, LC, or toxicity. Patients with central tumors were less likely to have acute grade greater than or equal to three toxicity than those with peripheral tumors (odds ratio: 0.24; $p = 0.02$).

Conclusions: Central tumor location did not predict for inferior OS, LC, or toxicity following SBRT when a lower mean BED was utilized.

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Stereotactic body radiotherapy (SBRT) has been increasingly utilized in the management of medically inoperable early stage non–small-cell lung cancer (NSCLC). For peripheral tumors, the Radiation Therapy Oncology Group (RTOG) 0236 phase II trial demonstrated a 3-year primary tumor control of 97.6% and 3-year lobar control of 90.6% when a dose of 54 Gy was delivered in three fractions.[1] However, there is considerable concern that treatment of centrally located tumors could lead to increased toxicity. A phase II trial at the University of Indiana noted increased grade 3–5 toxicity for patients with central tumors (within 2 cm of the proximal bronchial tree) compared with peripheral tumors (27.3% versus 10.4%; $p = 0.09$) using SBRT prescribed to at least 54 Gy in three fractions (corrected for tissue heterogeneity).[2,3] This led to the exclusion of patients with central tumors from RTOG 0236, as well as the formulation of a separate dose escalation study for central tumors using a lower biological equivalent dose (BED; RTOG 0813).

Experience in treating central tumors with SBRT suggests that regimens using more than three fractions may be reasonably well tolerated.[4–7] However, decreasing the BED with a more conservative dose-fractionation regimen could be concerning for decreased local control (LC) and possibly overall survival (OS). Two large multiinstitutional studies have suggested that a BED of at least 100–105 Gy may be necessary to achieve optimal LC outcomes,[8,9] although another multiinstitutional tumor control probability model has suggested greater LC with a BED of 151.2 Gy (54 Gy in three fractions) compared with 100 Gy (50 Gy in five fractions).[10]

The aim of this study was to examine a large, single-institution experience with SBRT for both peripherally and centrally located NSCLC. Our goal was to assess whether or not central tumor location would predict for worse OS, LC, or acute and late toxicity in an era of more conservative dose-fractionation regimens for centrally located tumors.

PATIENTS AND METHODS

Patient Selection

We prospectively maintained an institutional database of patients treated with SBRT for primary NSCLC from September 2007 to August 2013. From this database, we selected all patients with AJCC 7th edition stage cT1-2N0M0 disease, who had at least one follow-up appointment with medical oncology, radiation oncology, or pulmonology. Central tumor location was defined as within 2 cm of the proximal bronchial tree (RTOG definition[2]) or within 2 cm of the heart, trachea, pericardium, or vertebral body, but 1 cm away from the spinal canal (based on a modification of the MD Anderson Cancer Center definition[4]).

Treatment

Patients were immobilized in a customized full-length vacuum cushion and underwent a four-dimensional computed tomography (CT) scan during free breathing. Abdominal compression was used only for select cases in which tumor excursion exceeded 1 cm. An internal target volume was contoured to include the entire respiratory excursion of the tumor using the Advantage Workstation (GE Healthcare, Waukesha, WI). An isovolumetric 7 mm expansion was added to the internal target volume create a planning tumor volume (PTV). The heart, lung, esophagus, proximal tracheobronchial tree, spinal cord, and brachial plexus were contoured.

Treatment plans were generated using Eclipse (Varian Medical Systems, Palo Alto, CA), with tissue heterogeneity corrections based on the anisotropic analytical algorithm. Priority was given to PTV coverage, at the expense of normal tissue exposure. All plans were normalized such that 95% of the PTV was covered by 100% of the prescription dose and 99% of the PTV was covered by at least 90% of the prescription dose, with an expected maximum heterogeneity of 111–143% within the tumor (corresponding to 70–90% of the maximum dose at the edge of the PTV). A higher priority was given to obtaining full coverage of the PTV to the prescription dose than to remaining within RTOG guidelines for organs at risk. Patients were treated initially with multiple nonopposed, noncoplanar beams, or more recently with a dynamic conformal arc technique (described in detail by Ross et al.[11]). Intensity-modulated radiation therapy using static fields or volumetric modulated arc therapy was reserved for the minority of cases when forward planning resulted in an inferior plan.

All patients were treated in three to five fractions on nonconsecutive days, completing therapy within 15 calendar days. Cone-beam CT image guidance was used for all patients.

Follow-Up

Follow-up included a history and physical examination approximately 4 weeks after completing SBRT. Patients were then evaluated clinically and with a noncontrast chest CT every 3 to 4 months for the first year, then every 3–6 months thereafter. Local failure was defined as a recurrence within the treated lobe as determined by biopsy or clinical judgment of the treating physician. OS was recorded based on most recent evidence of vital status in the medical record or by death date, based on obituary or in-hospital death. LC and toxicities were followed as of last radiographic or clinical follow-up.

Treatment-related toxicity was scored with the National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. An acute toxicity was defined as a treatment-related side effect occurring within 90 days of the first fraction; a late toxicity was one that occurred after this time.

Data Analysis

The BED was calculated using the linear quadratic equation, assuming $\alpha/\beta = 10$. For univariable analysis, the χ^2 test was used for categorical variables, and the student's t test was used for continuous variables. The Kaplan–Meier method was used to estimate OS and LC. Subgroups were compared with the log-rank test. Additional univariable and multivariable analyses for time-to-event analyses were performed using Cox proportional hazards modeling. Acute toxicity and late toxicity were evaluated with the χ^2 test and multivariable logistic regression modeling. Multivariable analyses adjusted for potential covariates, including patient factors like age, sex, and performance status; clinical factors like biopsy versus nonbiopsy diagnostic method, tumor histology, tumor size, and T-stage; and treatment-related factors like BED, total number of targets, maximum lung point dose, mean lung dose, volume of lung receiving greater than or equal to 5 Gy (V5), volume of lung receiving greater than or equal to 10 Gy (V10), and volume of lung receiving greater than or equal to 20 Gy (V20). All analyses were performed with SPSS version 19 (IBM, Armonk, NY).

This study was granted approval from the institutional review board at our institution.

RESULTS

There were 251 patients with 272 tumors included in this analysis, among whom 111 patients (44.2%) received SBRT for centrally located tumors. Median follow-up was 31.2 months for OS and 21.4 months for all other outcomes. A total of 181 patients (72.1%) had biopsy-proven NSCLC, and 82 patients (32.7%) had invasive mediastinal staging. Patients with central tumors were more likely to be older (mean 75.8 versus 73.5 years; $p = 0.04$), have larger tumors (mean 2.5 cm versus 1.9 cm; $p < 0.001$), undergo invasive mediastinal staging (46.8% versus 21.4%; $p < 0.001$), and be treated with a lower BED (mean 120.2 Gy versus 143.5 Gy; $p < 0.001$) compared with those with peripheral tumors. The BED used for peripheral tumors was 151.2 Gy (54 Gy in three fractions) in 80.0% of patients, whereas BED for central tumors was more variable (151.2 Gy in 36.9% of patients, 112.5 Gy [50 Gy in four fractions] in 30.6% of patients, and 100 Gy [50 Gy in five fractions]) in 17.1% of patients. There were no other significant differences in patient, clinicopathologic, or treatment-related factors between patients with central versus peripheral tumors (Table 1).

